

New advances in stem cell research: practical implications for regenerative medicine

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KEY WORDS

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ABSTRACT

Regenerative medicine is searching for stem cells that can be safely and efficiently employed for regeneration of damaged solid organs (e.g., the heart, brain, or liver). Ideal for this purpose would be pluripotent stem cells, which, according to their definition, have broad potential to differentiate into all types of adult cells. For almost 20 years, there have been unsuccessful attempts to harness controversial embryonic stem cells (ESCs) isolated from embryos. Induced pluripotent stem cells (iPSCs), generated by genetic modification of adult somatic cells, are a more promising source. However, both iPSC and ESCs are associated with a risk of teratoma formation. At the same time, various types of more-differentiated adult stem and progenitor cells derived from the bone marrow, umbilical cord blood, mobilized peripheral blood, or fat tissue are being employed in clinical trials to regenerate damaged solid organs. However, for most of these cells, there is a lack of convincing documentation for successful regeneration of the treated organs. Beneficial effects of those cells might be explained by paracrine effects of growth factors, cytokines, chemokines, bioactive lipids, and extracellular microvesicles, which are released from the cells and have trophic, antiapoptotic, and angiopoietic effects. Nevertheless, there is evidence that adult tissues harbor a promising population of very rare dormant stem cells with broad differentiation potential. In this review, we will discuss various potential sources of stem cells for regenerative medicine and the mechanisms that explain some of their beneficial effects as well as highlight the results of the first clinical trials.

Introduction Current clinical results with stem cell therapies, except in the field of hematopoietic transplants, remain mostly in the realm of wishful thinking. However, evidence has accumulated that stem cell therapies are moving in the right direction, and there is justifiable hope that more efficient strategies will be developed in the near future. On this basis, therapeutic strategies employing stem cells have been proposed as alternative therapies for a multitude of damaged organs such as the myocardium after heart infarction, brain after stroke, spinal cord after mechanical injury, age-related macular degeneration of the retina, damaged liver, extensive skin burns, diabetes, and Parkinson disease.¹⁻⁷ It is believed that technologies leading to optimization of the clinical use of stem cells in the new and developing clinical discipline of regenerative

medicine will become the keys to improving life quality and increasing human life span.

Overall, there are 2 important goals of regenerative medicine. The first is to employ stem cells efficiently and safely in therapies for injured organs and tissues. It is believed that, in the future, the transplantation of the entire organs will be largely replaced by the transplantation of a suspension of stem cells directed to the given organ, alone or in combination with organic or synthetic scaffolds, which will perform the task of rebuilding the injured tissues.⁸ However, there is also a second important and parallel goal of regenerative medicine that is widely understood. Since stem cells are continuously regenerating our tissues and playing a crucial role in the replacement of senescent and used-up somatic cells, an important goal is to develop strategies that will improve

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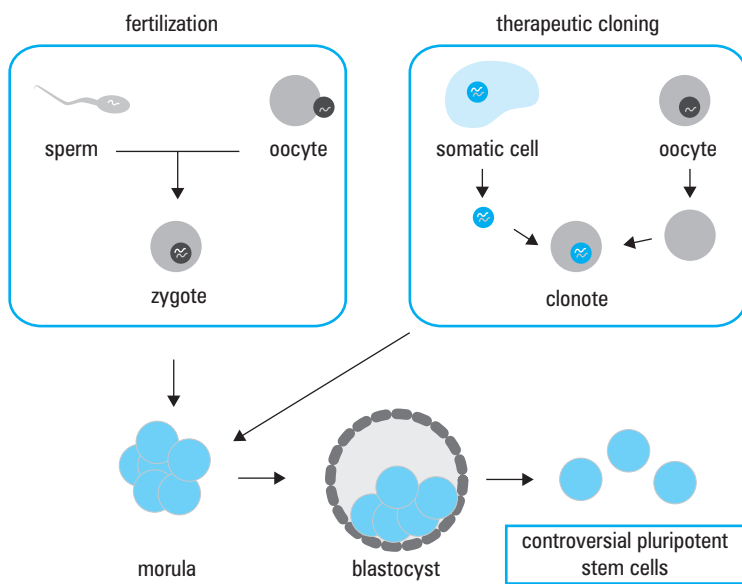


FIGURE 1 Pluripotent stem cells (PSCs) obtained from embryos; PSCs isolated from zygote-derived blastocysts in the normal process of fertilization; PSCs can also be obtained by means of so called therapeutic cloning, as the result of transfer of the nucleus from adult somatic cells into an enucleated oocyte

the quality of life and longevity by improving the regenerative potential and proper functioning of adult stem cells residing in various organs.⁹

In seeking our first goal, we need to identify a population of stem cells that will be able to differentiate into all types of adult cells and design efficient strategies to reconstruct the 3-dimensional structure of damaged tissue, or, which even today sounds like science fiction, to grow an entire organ in a dish. As another goal, we need to unravel the mechanisms that effectively maintain the population of stem cells throughout life and that prevent their senescence and thus their potentially premature depletion from adult tissues. No tissue can regenerate if the stem cells are not functioning properly.

In this review, we will first present the current strategies creating or isolating embryonic stem cells (ESCs) for the purposes of regenerative medicine. We will discuss the pros and cons of using such cells and explain why these cells are not employed in the clinic. Next, we will introduce the various types of stem cells isolated from adult tissues, including some rare populations of early-development stem cells. We will also discuss the advantages and disadvantages of using adult tissue-derived cells in regenerative medicine and highlight the results of the first clinical trials.

Finally, we will focus on the development of preventive and therapeutic strategies to maintain the population of adult stem cells in vital organs under optimal conditions for tissue and organ rejuvenation and regeneration throughout life. It is entirely true that a healthy stem cell compartment is required to maintain a healthy body.

Search for a noncontroversial, safe, and efficient source of stem cells for regenerative medicine For the purposes of regenerative medicine, the ideal stem cells would be pluripotent stem cells (PSCs) or multipotent stem cells (MultSCs), which, according to their definition, have a broad potential to differentiate into cells from all 3 germ layers

(meso-, ecto-, and endoderm) in the case of PSCs or from 2 germ layers in the case of MultSCs.¹⁰ Based on encouraging data in experimental animals, several types of stem cells isolated from embryonic and adult tissues hold a more-or-less justified promise for treating patients. Thus, we will discuss the pros and cons for both ESCs and nonembryonic sources of stem cells, including induced PSCs (iPSCs) and stem cells isolated from adult tissues.

Pluripotent stem cells derived from embryos There are 2 potential sources of PSCs isolated from embryos (FIGURE 1), namely, those isolated from surplus embryos stored in in-vitro fertilization clinics or PSCs obtained by employing nuclear transfer to oocytes in the process of so called therapeutic cloning.^{1,10-12}

ESCs are pluripotent stem cells isolated from embryos. As mentioned above, early-development embryonic tissues are a potential source of PSCs, and such cells can be obtained from the developing morula or blastocyst using, for example, frozen surplus embryos that are stored in in-vitro fertility clinics (FIGURE 1). By this means, several human ESC lines have been established.¹³ Unfortunately, obtaining PSCs from stored frozen human embryos for therapeutic purposes is controversial, and it is well known that there will be differences in tissue histocompatibility between stem cells derived from such embryos and potential recipients. Specifically, because the embryo has inherited a unique set of parent-derived HLA antigens,¹¹ ESCs will differentiate into cells with different sets of histocompatibility antigens than the potential recipient and will be recognized by the immune system of the recipient as allogeneic. Moreover, these cell lines have been demonstrated to change their properties over time in culture. Also, given the ethical and technical considerations, it is hard to imagine obtaining such embryos on demand for a specific patient from biological parents who want to save one of their children. Finally, studies in experimental animals as recipients of such cells have demonstrated that administration of established ESC lines may lead to the development of teratomas.¹⁴

Pluripotent stem cells obtained as a result of therapeutic cloning Taking into consideration the ethical aspects and technical problems in obtaining normal human embryos and with the awareness that ESCs received from such embryos will differentiate into tissues that are not histocompatible with the recipient's tissues, an alternative strategy has been developed for obtaining histocompatible PSCs in the laboratory as a result of so called therapeutic cloning. The strategy of therapeutic cloning requires a donor ovum and consists in creating a cell in vitro called a clonote (FIGURE 1), which is equivalent in developmental potential to a zygote (fertilized oocyte).¹¹⁻¹⁵ During the creation of clonotes, the nucleus is removed from the donated oocyte, and the cytoplasm of the ovum is

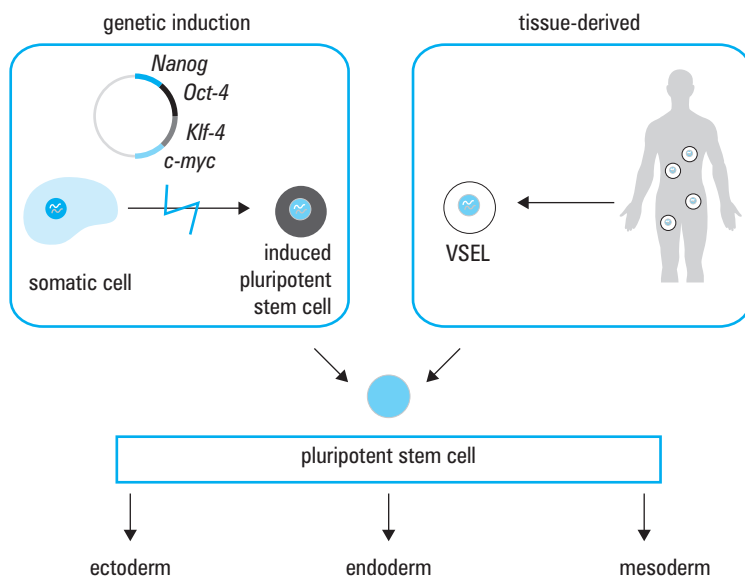


FIGURE 2 Pluripotent stem cells (PSCs) obtained from postnatal tissues; PSCs can be obtained by transforming somatic cells (e.g., fibroblasts) using genes that encode embryonic transcription factors (e.g., *Oct-4*, *Nanog*, *Klf-4*, *c-myc*); PSCs or multipotent stem cells can also be obtained from adult tissues (e.g., very small embryonic-like stem cells [VSELs])

used as a biochemical incubator to dedifferentiate the injected patient-derived somatic cell nucleus (e.g., from a fibroblast or lymphocyte). After transfer (microinjection) of the somatic cell nucleus into the cytoplasm of the ovum, the microinjected chromosomes undergo dedifferentiation. All of this leads to the loosening of chromatin structure and to the return of developmentally differentiated DNA derived from the donor's somatic cell to the state it had in the fertilized ovum. These clonotes generated by nuclear transfer are, like the fertilized ovum, totipotent, and artificially created embryos derived from such cells are a potential source of PSCs when the embryo develops into a morula or blastula. What is most important, such cells will be histocompatible with the donor of the nucleus employed in therapeutic cloning.¹¹ Thus, this is a potential strategy for generating "custom-made" PSCs for therapy. Nevertheless, besides some ethical concerns, the main obstacles to a broader usage of therapeutic cloning are the necessity of obtaining human oocytes and discouraging observations that PSCs derived from clonotes, such as ESCs, create teratomas.¹⁴

On the other hand, if a clonote is placed in the uterus, it can, like a zygote, give rise to a new individual. This is the basis for so called reproductive cloning, which, at least for human application, is highly dangerous and widely considered to be unethical.^{15,16} Recall that reproductive cloning employing nuclear transfer was the basis for creating Dolly the sheep.

Pluripotent and multipotent stem cells derived from somatic postnatal cells The controversy around ESCs has forced scientists to search for other non-controversial sources of PSCs. Below, we will discuss the strategy for generating iPSCs as well as attempts to purify PSCs or MultSCs from adult tissues.

Induced pluripotent stem cells These noncontroversial (from an ethical point of view) stem cells are derived by genetic modification of mature postnatal somatic cells (FIGURE 2) by their transformation in vitro using genes encoding key transcription factors for the development of ESCs (*Oct-4*, *Nanog*, *Klf4*, *c-myc*). These genes are introduced into the somatic cells (e.g., fibroblasts) using retroviral vectors.^{1,11,12} As a result of this strategy, a transformed cell can be obtained that can differentiate into cells derived from all 3 germ layers. However, such transformation is relatively rare because on average 1 cell in several thousands undergoing the aforementioned genetic manipulation yields to transformation (is induced to the embryonic stage) and begins to proliferate, creating a clone consisting of iPSCs.¹² Recently, some modifications to this strategy have been described that employ more limited numbers of genes in the transduction process, microRNA (miRNA), or even small molecules.¹² Surprisingly, similar effects have been recently obtained by stressing somatic cells with a mildly acidic bath or even vigorous trituration to generate stimulus-triggered acquisition of pluripotency cells.¹⁷ However, this process for generating iPSCs is difficult to control, and the cells obtained as a result of this strategy, such as ESCs obtained from embryos, also create teratomas in experimental animal models.¹⁴ This problem must be solved prior to the clinical use of such cells. Furthermore, the transduction of genes into somatic cells as a step in generating iPSCs additionally disturbs the structure and organization of the DNA, which in turn may lead to mutations and growth of neoplastic cells.¹⁸ It has also been reported that iPSCs are potentially immunogenic and rejected by the recipient immune system.¹⁹ Nevertheless, iPSCs have been proposed as an ethically acceptable source of PSCs that are an alternative to ESCs isolated from embryos.

The creation of iPSCs is not burdened with the problem of obtaining human ova, and, most importantly, the cells generated from iPSCs will have the same histocompatibility genes as the potential recipient. In a recent report, iPSCs were reported to have a totipotent character similar to that of a fertilized oocyte.²⁰ This potential to give rise to both the embryo and placenta may again raise issues concerning the ethical derivation of such normal transformed (induced to totipotency) cells.

Cells with pluripotent and multipotent stem cell characteristics isolated from adult postnatal tissues Cumulative evidence from several laboratories shows that very rare cells that express some early-development embryonic markers may reside in adult tissues,¹¹ indicating their close relationship to the early stages of embryonic development. In support of the presence of early-development stem cells in postnatal life, several types of putative PSCs/MultSCs have been described and isolated, primarily from the bone marrow (BM),

which are able to give rise to cells from more than 1 germ layer.¹¹ These cells were isolated by employing various strategies such as ex-vivo expansion of partially purified cells by immunomagnetic or fluorescence activated cell sorting.²¹⁻²⁹ However, in most of the expansion cultures, the rare cells that were able to initiate expansions and cross-germ layer commitment were not characterized at the single-cell level,¹¹ and in most of these cases, the phenotype of the putative PSCs/MultSCs with stem cell-like properties was described ex post facto after phenotyping the clones of already differentiated in vitro-expanded cells.¹¹ Nevertheless, many investigators would agree that if early-development stem cells endowed with broader differentiation potential reside in adult tissues, they are all probably closely related and exist at different levels of tissue specification. Most likely, they represent overlapping populations of early-development stem cells that, depending on isolation strategy, ex-vivo expansion protocol, and the markers employed for their identification. These cells have been given different names, such as multipotent adult stem cells,²¹ mesenchymal stem cells (MSCs),²² multilineage-differentiating stress-enduring (Muse) cells,²³ multipotent adult progenitor cells (MAPCs),²⁴ unrestricted somatic stem cells (USSCs),²⁵ marrow-isolated adult multilineage-inducible cells,²⁵ multipotent progenitor cells,¹¹ spore-like stem cells,²⁷ and, as described by my team, very small embryonic-like stem cells (VSELs).^{28,29}

Overall, the presence of PSCs/MultSCs in adult tissues can be explained by the possibility that early during embryogenesis not all of the earliest-development stem cells disappear from the embryo after giving rise to monopotent tissue-committed stem cells (TCSCs), but some survive in developing organs as a dormant backup population of stem cells.^{10,11} These cells could give rise to TCSCs and thus be involved in tissue/organ rejuvenation and in organ regeneration following organ injury. In support of this notion, evidence has accumulated that adult murine tissues do in fact contain, in addition to rapidly proliferating stem cells, a backup population of more primitive dormant stem cells.^{10,11} These cells, expressing primitive phenotypes, are detected during tissue/organ injuries (e.g., heart infarct, stroke, or skin burns) as a population of circulating early-development stem cells in peripheral blood.³⁰⁻³³

Other sources of differentiated tissue-committed stem cells isolated from postnatal tissues

From a historical point of view, hematopoietic stem cells (HSCs) were the first stem cells to be employed in the clinic, and they have been successfully used for more than 40 years. HSCs are an example of already differentiated monopotent TCSCs for lympho-hematopoietic cells.³⁴ Such cells are relatively easily isolated from the BM, mobilized peripheral blood (mPB), or umbilical cord blood (UCB). Of note, for several years, HSCs have been wrongly

considered to exhibit stem cell plasticity, allegedly changing their commitment from hematopoietic tissue to other types of tissues. This will be addressed in the subsequent sections of this review.

Other sources of adult stem cells For the purposes of regenerative medicine, non-HSCs may also be isolated from adipose tissue or expanded ex vivo from biopsies of the epidermis, skeletal muscle, or even atrial myocardium.^{1,4} Conversely, owing to obvious ethical and technical considerations, it is much more difficult to obtain stem cells from the myocardium, liver, pancreatic islets, or neural tissue of healthy donors compared with stem cells isolated from liquid hematopoietic tissues (BM, mPB, or UCB).

Therapeutic effects of stem cells isolated from adult tissues after the “stem cell plasticity era”

Stem cells isolated from adult tissues (BM, mPB, and UCB) are currently widely employed in hematopoietic transplants. However, the same cells are also employed in trials to regenerate damaged nonhematopoietic organs. The beneficial effects of these cells in other clinical settings, e.g., heart infarct, were based on experimental data in animal models and, for many years, were misinterpreted. As a result, a few years ago, a concept was proposed that HSCs are plastic and may extensively transdifferentiate into cells from different germ layers. These observations initiated several clinical trials where cells isolated from hematopoietic tissues, mostly the BM, were employed for tissue/organ regeneration.

However, the concept of stem cell plasticity has been abandoned, and alternative hypotheses have been proposed to explain the beneficial effects of stem cell therapies. First, it is possible that some of the beneficial stem cell plasticity data can be explained by the phenomenon of cell fusion.^{35,36} Specifically, transplanted HSCs might undergo fusion (melding) with the cells of the injured organs. If so, cells in the injured organs treated with transplanted HSCs would be heterokaryons, expressing double the number of chromosomes, and are created as a result of the fusion of transplanted HSCs with cells belonging to the injured organ. However, cell fusion is extremely rare and cannot fully account for the extensive positive transdifferentiation/plasticity data claimed in several reports.

Importantly, some positive effects of stem cell therapies that are beneficial for tissue/organ injuries have been explained by alternative mechanisms, such as paracrine effects of stem cells employed in therapy owing to released growth factors, cytokines, chemokines, and extracellular microvesicles. Alternatively, it has been proposed that BM-, mPB-, and UCB-derived stem cells employed for therapy may, from the beginning, contain heterogeneous populations of stem cells, including some very rare PSCs or MultSCs. These 2 alternative explanations of stem cell plasticity will be discussed in more detail below.

Paracrine effects of stem cell therapies As mentioned above, the positive effects of cell therapies might be explained by the involvement of stem cell-derived paracrine effects. We already demonstrated in the past that stem cells employed in therapy are a rich source of growth factors, cytokines, chemokines, and bioactive lipids that may inhibit apoptosis and promote neovascularization in the damaged tissues.^{37,38} Paracrine signals may also activate local TCSCs. A growing body of evidence suggests that paracrine effects of cells employed as therapeutics in regenerative medicine could be more efficiently exploited to optimize cell-based therapies, which could be achieved by ex-vivo manipulation of cells to enhance the secretion of proregenerative factors. Theoretically, this could be accomplished by exposure of cells to hypoxia prior to infusion and delivery to the injured organ or by transduction of these cells by expression vectors that increase the secretion of proangiopoietic factors (e.g., vascular endothelial growth factor or fibroblast growth factor 2).

In addition to soluble factors secreted by stem cell therapeutics, both the function and phenotype of the target cells in the damaged tissues may also be modified by the transfer of cell receptors, cytoplasmic proteins, mRNA, and miRNA by extracellular microvesicles (ExMV)—the spherical structures in which a part of the cell cytoplasm enriched for these molecules is released from the cells encapsulated by the cell membrane.³⁸⁻⁴⁰ Therefore, ExMVs released from the surface of cells employed to regenerate damaged organs may deliver this biologically important cargo to damaged tissues. Evidence has accumulated that ExMV cargo has positive effects on cell survival and angiogenesis. Thus, paracrine effects associated not only with soluble factors released from cells but also associated with ExMVs most likely make the major contribution to the positive results reported in clinical trials employing adult stem cells. Moreover, recent data show that ExMVs may replace whole cells for therapy. In support of this possibility, MSC-derived ExMVs were found to have the same beneficial effect of protecting the kidney against ischemia reperfusion-induced acute and chronic kidney injury.^{41,42}

Thus, since ExMVs have similar beneficial effects in regenerative therapy as the intact cells from which they are derived,^{41,42} producing ExMVs on a large scale and even modifying their composition should be considered.⁴⁰ Several possibilities for modifying ExMVs are shown in **FIGURE 3**. First, it should be possible to expand ExMV-producing cell lines that lack genes encoding histocompatibility antigens to generate HLA antigen-deficient ExMVs. This approach would minimize the possibility of cross-immunization with donor HLA antigens. Second, ExMV producer cell lines could be transduced with genes that overexpress growth factors that protect target cells in damaged organs from apoptosis and

stimulate proliferation of residual remaining cell populations or growth factors and cytokines that effectively induce angiogenesis. Third, ExMVs derived from cells cultured in hypoxic conditions could be enriched in mRNAs and miRNAs that promote angiogenesis. On the other hand, ExMV producer cell lines could be enriched for mRNA and regulatory miRNA species that, after delivery to the damaged tissues, would promote regeneration. Finally, we envision that ExMV producer cell lines could be manipulated to be enriched for molecules that would facilitate tropism of ExMVs to the specific damaged organs and tissues.

Heterogenous populations of stem cells in adult tissue

Finally, it must be considered that cells employed for therapy derived from, e.g., hematopoietic tissues may, from the beginning, contain populations of early-development stem cells, including rare PSCs or MultSCs such as VSELs that demonstrate a broader differentiation potential.^{28,29,43} These cells are most likely responsible for the rare events of donor-derived chimerism after infusion of BM, mPB, or UCB cells. VSELs have so far been isolated successfully in several laboratories and have been demonstrated to give rise to cells of all 3 germ layers.⁴³⁻⁴⁸ However, the fact that VSELs are protected from uncontrolled proliferation by epigenetic changes affecting insulin/insulin-like growth factor signaling (IIS) explains their high quiescence and very low incidence of chimerism after transplantation. Therefore, intensive studies are being conducted in several laboratories worldwide to modify their imprinting and to expand these rare cells for application in regenerative medicine.

Similarly, there have been attempts to employ in the clinic other types of nonhematopoietic stem cells isolated from adult tissues that are closely related to VSELs, such as Muse cells, USSCs, MAPCs, and MSCs. As mentioned above, it is most likely that these are all overlapping populations of early-development stem cells.

Current clinical applications of stem cells

Adult tissue-purified and expanded stem cells have been the only stem cells widely employed in the clinic so far. What is currently most important is to resolve issues concerning the optimal cell type to be employed for regeneration of damaged tissues, its dosage, and the route and timing of administration. Another important aspect is to proceed with rigorous, large-scale, rationally designed, randomized clinical trials employing cell therapeutics in particular clinical settings. In this review, we omit clinical applications of HSCs for hematopoietic transplants, because this has been a well-established field for 45 years, and focus on the application of stem cells for regeneration of nonhematopoietic organs and tissues. Stem cells alone or in combination with scaffolds are now employed in their first clinical trials. In this review, we will highlight the most important

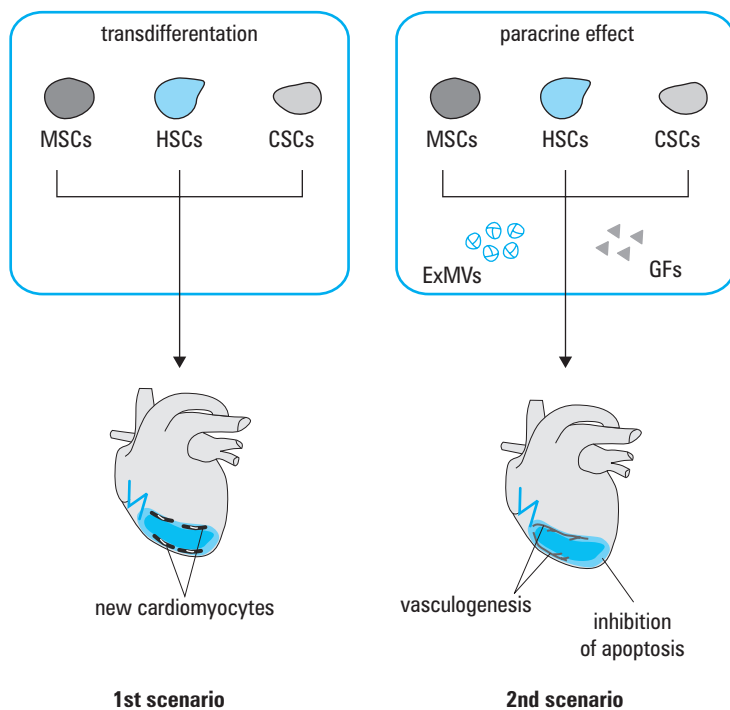


FIGURE 3 Two possible scenarios illustrating the beneficial effects of stem cell therapies in regenerative medicine in the example of heart infarct. First scenario: cells employed for therapy (e.g., cardiac stem cells [CSCs]; hematopoietic stem cells [HSCs]; or mesenchymal stem cells [MSCs]) may theoretically transdifferentiate into cardiomyocytes. However, if this occurs at all, it is a very rare and random phenomenon and is not well substantiated by current experimental data. Second scenario: cells employed for therapy (e.g., CSCs, HSCs, or MSCs) do not transdifferentiate into cardiomyocytes but secrete several paracrine growth factors (GFs) and shed extracellular microvesicles (ExMVs), which inhibit apoptosis in damaged myocardium and stimulate angiogenesis. Evidence is accumulating that this is a major effect in the currently employed stem cell therapies.

of those therapies. However, they are all still under development, often only feasibility studies have been performed, and we still need to wait for long-term results to be reported.

Applications of stem cells in clinical cardiology

Cardiovascular disease continues to be one of the main causes of death worldwide, and despite improved outcomes of patients with acute myocardial infarction (AMI), the incidence of heart failure (HF) increases. Because AMI leads to a substantial and irreversible loss of cardiomyocytes, there is clearly a need for new therapies, which could restore the myocardial structure and function.^{1,49} Cell therapies have been used in patients with AMI, HF, refractory angina, as well as critical limb ischemia and claudication. In the past 13 years, numerous clinical studies have been performed, in particular in patients with AMI. Several types of cells were used, isolated either from the BM or adipose tissue. In the majority of trials, a heterogenous population of mononuclear cells isolated by Ficoll centrifugation was used, which consists of differentiated cells as well as HSCs and endothelial progenitor cells. Subsequently, some other populations of more purified BM stem cells have been employed in the clinic, such as CD34⁺CXCR4⁺ and CD133⁺ cells.⁵⁰ However,

based on the lack of convincing evidence showing new donor-derived cardiomyocytes derived from highly purified BM-derived stem cells, it has been recently proposed that the potential paracrine effect of BM-derived cells play a crucial role in the regeneration of damaged myocardium by proangiogenic, anti-inflammatory, and antiapoptotic actions.⁵¹⁻⁵³ From a historical point of view, the first small nonrandomized clinical trials using BM-derived cells in ST-segment elevation myocardial infarction showed a modest but significant improvement of the left ventricular ejection fraction (LVEF). More recent trials with magnetic resonance imaging (MRI) for the assessment of the LVEF, including the Polish REGENT trial, indicated that while treatment with BM cells did not lead to a significant improvement of LVEF or LV volumes in patients with AMI and impaired LVEF, there was a trend in favor of cell therapy in patients with most severely impaired LVEF.^{52,53} The most recent meta-analysis confirmed that when the most accurate method of cardiac imaging is used (MRI), there is no benefit of cell therapy in patients with AMI.^{54,55} The long-term follow-up BAMI trial to confirm safety of the cell therapy was designed to verify, among others, the effect of this treatment on long-term survival and potential causes of mortality (NCT01569178). At present, it would be premature to use cell therapy in patients with AMI in routine clinical practice. In patients with HF, cell therapy has been shown to improve LVEF and remodeling as well as the clinical status. These results have to be interpreted as hypothesis-generating and need verification in large randomized clinical trials with long-term follow-up.^{1,49,56} Also, for HF patients with severely impaired LVEF and large areas of myocardial scar, new types of cells with improved differentiation capacity, such as cardiopoiesis-guided MSC, might be beneficial.⁵⁷ In patients with HF, adipose tissue-derived mesenchymal stem cells are being used, and recently so called cardiac stem cells were isolated and expanded from small atrium biopsies. However, these cells are very poorly defined and recently have become the subject of controversy about whether they are truly stem cells. Therefore, cardiologists still await the development of a stem cell population that will be safe and effective for use in the clinic. In our opinion, patients with refractory angina and no possibility of revascularization might be a population in which the use of cell therapy with electromechanical mapping to target the viable hibernating myocardial segments might prove clinically beneficial (improved symptoms and exercise tolerance and better perfusion).⁵⁸ However, this population is less than 2% of patients with coronary artery disease. The crucial issues to progress the field is to standardize the cell product, which would allow to compare the results of the trials and to identify the cells with the highest reparatory potential.

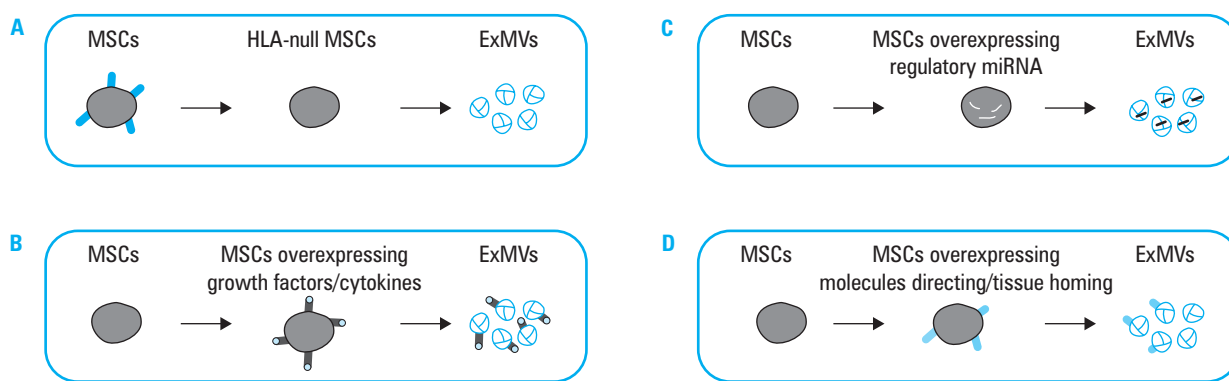


FIGURE 4 Different approaches to generating more efficient proregenerative ExMVs in vitro. ExMVs can be harvested from large-scale in vitro cultures of ExMV-producing cell lines. Such cell lines may be modified to obtain ExMVs that **A** – do not express HLA antigens, **B** – are enriched in growth factors, cytokines, and chemokines that promote regeneration of damaged organs, **C** – are enriched in mRNAs and regulatory micro RNAs (miRNAs) facilitating regeneration of damaged tissues and/or promoting angiogenesis, and **D** – display molecules that direct them to the damaged tissues.

Applications of stem cells in neurology Brain damage (e.g., stroke) and spinal cord injury as well as several neurodegenerative disorders, including Parkinson disease, amyotrophic lateral sclerosis, and Alzheimer disease, are potential targets for stem cell therapies.^{4,5} Several preclinical animal models indicate the feasibility of such treatments. Stroke is the third leading cause of death and disability in developed countries. Several clinical trials are currently registered to ameliorate the side effects of stroke using autologous HSCs, BM-derived MSCs, and adipose tissue-derived MSCs. Cells are injected into patients intracerebrally, intra-arterially, or intravenously. In parallel, stem cells are also employed in patients after spinal cord injury. For this application, autologous BM-derived cells or even fetal olfactory mucosa-derived cells are employed. These are mostly feasibility studies, and we need to wait for long-term results from these trials. It is also important to note that a clinical trial that involved ESC-derived neural cells for spinal cord injury performed in the United States by the Geron company was ended prematurely because the cells employed in patient therapy were growing tumors in experimental mice.^{4,5,12} Alzheimer disease is the most frequent form of dementia, characterized by memory loss and cognitive decline, and there are currently 2 different clinical trials to evaluate the paracrine effect of intracerebral and intravenous infusion of MSCs derived from the human UCB. An important target for stem cell therapy is amyotrophic lateral sclerosis, which is a fatal neurological disease characterized by degeneration of upper and lower motor neurons, for which there is currently no clinically impactful treatment.⁵⁹ In most of the clinical trials, BM-derived mesenchymal stem cells are employed, although recently, a trial was initiated using spinal cord-derived neural stem cells. At this point, it is too early to draw conclusions regarding the long-term effects of such therapies.^{4,5,12,59-61}

Applications of stem cells in ophthalmology Stem cell therapies for retinal disease are underway, and several clinical trials are recruiting patients to treat diseases such as age-related macular degeneration, Stargardt disease, and retinitis pigmentosa, for which there are currently no curative treatments.^{3,62} In most of these trials, autologous BM-derived HSCs are being employed, and a clinical trial has been initiated recently using patient-derived VSELs. Age-related macular degeneration and Stargardt disease are also potential targets for ESC-derived retinal pigment epithelium cell lines, and stem cell-based treatments have already been performed on patients. In contrast to ESC-derived cell lines, iPSCs cannot be applied in patients with Stargardt disease because such patient-derived iPSCs will carry the mutation responsible for this disease. Another problem, as discussed above, is that both ESCs and iPSCs carry the risk of teratoma formation.¹⁴

Other clinical applications In addition to cardiovascular, neurological, and ophthalmological applications, the field of regenerative medicine is trying to employ adult tissue-derived stem cells for the treatment of bone, connective tissue, and articular lesions in orthopedics as well as wound healing, and new applications are emerging, such as the treatment of infertility, liver damage, diabetes, peripheral artery diseases, and even baldness.¹⁻⁸ This list of possible applications has been expanding over time. However, we again emphasize that most of the currently observed effects with the available stem cells are due to the paracrine effects of such cells in therapy (FIGURE 4).

Potential strategies to increase the robustness of adult stem cells in adult tissues It is known that TCSCs in adult tissues work hard throughout the entire lifetime of an individual. As examples, it is known that the intestinal epithelium is replaced every 48 to 72 hours, the epidermis every 14 days, and granulocytes every few days, whereas erythrocytes have a physical half-life of 100 to 150 days.¹¹

The replacement of depleted cells is slower in other organs and tissues; nevertheless, it has been shown that even such organs as the heart and brain exhibit slow biological regeneration. It is hard to imagine that a cell could live in an organ for 80 years without being replaced.

Taking into consideration the enormous potential of TCSCs and the important role they play in everyday regeneration of several types of tissues, stem cells have become an object of extensive interest for clinicians and are considered key potential targets for modern pharmacology to improve the quality of life and extend lifespan.

However, the key target in all these considerations should be stem cells residing in adult tissues, which display several characteristics of PSCs/MultSCs.^{21-29,63} As mentioned above, these early-development stem cells are hypothesized to be a backup population for TCSCs.^{11,43} Evidence has accumulated that the quiescence of these cells (e.g., VSELs) is related to their epigenetically regulated resistance to IIS.⁹ It has been postulated that this mechanism prevents these early-development stem cells from premature depletion from adult tissues, which should result in their prolonged role as a source of TCSCs.

The link between the resistance of VSELs to IIS and their quiescence has implications for longevity and may also explain the beneficial effects of metformin and rapamycin, which interfere with IIS in the extension of lifespan. Calorie restriction and regular physical activity have similar effects on IIS. In fact, our recent results lend support to the hypothesis that calorie restriction and physical exercise both have a positive effect on the adult stem cell compartment, including the population of VSELs, and the number of VSELs correlates with extended lifespan and fertility in experimental animals. The positive effects of physical exercise and calorie restriction on adult stem cells have also been shown by other investigators for TCSCs such as HSCs,⁶⁴ neural stem cells,⁶⁵ and skeletal muscle satellite stem cells.⁶⁶

As already highlighted in this review, all these observations lend support to another important goal of regenerative medicine, which is the development of efficient strategies to increase the robustness of stem cells in adult tissues. It is also a challenge for modern pharmacology to develop more efficient drugs that will increase the resistance of early-development stem cells to IIS.

Conclusions Stem cells and their potential application in regenerative medicine is one of the hottest and most controversial areas in contemporary biology and medicine. Different stem cells have been proposed, but nobody at this point has identified a PSC that could be safely and efficiently employed in the clinic. Unfortunately, stem cell research is an area where patent issues and financial involvement of biotechnology companies is the basis for competition to the exclusion of cooperation. The incompetence of the public media, which is often the source of incorrect and

misleading information about this topic, has also had a negative impact on the field. On the other hand, preliminary reports about clinical trials are often overoptimistic, which we have recently experienced in the case of clinical trials using cardiac stem cells.⁶⁷

In summary, we tried to present the current topic of regenerative medicine in an unbiased way and explain why stem cell therapies may have a positive effect on damaged tissues, even if a significant level of donor-derived chimerism is not detected. Despite all the current limitations, the era of regenerative medicine is approaching, and the next years will bring exciting discoveries, leading to a broader application of stem cells in the clinic. Therefore, we should be optimistic about the future. We are now at a point of no return for stem cell therapies, but the road to the final goal will be bumpy and sometimes difficult.

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Postępy w badaniach nad komórkami macierzystymi: implikacje dla medycyny regeneracyjnej

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SŁOWA KLUCZOWE

komórki macierzyste embrionalne, klonowanie terapeutyczne, indukowane komórki pluripotencjalne, małe komórki macierzyste przypominające komórki embrionalne, efekty parakryne

STRESZCZENIE

Medycyna regeneracyjna poszukuje komórek macierzystych, które można efektywnie i bezpiecznie wykorzystać do regeneracji uszkodzonych narządów (np. serca, mózgu czy wątroby). Idealne w tym celu byłyby komórki pluripotencjalne, które wg definicji mogą się różnicować we wszystkie rodzaje dorosłych komórek. Od 20 lat bezskutecznie próbuje się zastosować kontrowersyjne embrionalne komórki macierzyste (*embryonic stem cells* – ESC) izolowane z zarodków. Bardziej obiecującym źródłem są tzw. indukowane komórki pluripotencjalne (*induced pluripotent stem cells* – iPSC) otrzymywane przez genetyczną modyfikację komórek dojrzałych. Niestety zarówno ESC i iPSC niosą ryzyko tworzenia potworniaków. Równolegle w badaniach klinicznych próbuje się wykorzystać w regeneracji narządów mięszsowych komórki macierzyste izolowane z dojrzałych tkanek np. komórki szpiku kostnego, krwi pępowinowej, mobilizowanej krwi obwodowej czy tkanki tłuszczowej. Niestety brakuje przekonujących dowodów dla większości z tych komórek, że mogą odtwarzać uszkodzone narządy mięszsowe. Obserwowane niewątpliwie pozytywne efekty tych komórek w terapii można wytłumaczyć wydzielaniem parakrynym szeregu czynników wzrostowych, chemokin, bioaktywnych lipidów oraz mikrofragmentów błonowych, które działają troficznie, antyapoptotycznie i proangiopoetycznie. Niemniej jednak istnieją dowody, że dorosłe tkanki kryją "uśpione" wczesne rozwojowo komórki macierzyste o szerokim spektrum różnicowania. W niniejszym artykule omówimy różne potencjalne źródła komórek macierzystych, które mogą zostać wykorzystane w medycynie regeneracyjnej oraz mechanizmy pozwalające wyjaśnić pozytywne efekty ich działania, a także przedstawimy wyniki pierwszych badań.

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