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Letter to the Editor

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Some Aspects of Stem Cell Therapy

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This short report is an overview of recent literature on stem cells and cell therapies. Certain papers tend to exaggerate positive effects leaving adverse events out of attention. Therefore, conclusions are partly based here on theoretic considerations. There is a discrepancy between the supposed ability of exogenous stem cells to migrate and engraft in tissues, differentiate along various cell lineages, and the absence of clear morphological evidence in vivo. Some papers discuss rejuvenation, replacement of senescent and damaged cells; others explain reported beneficial effects by paracrine or immunomodulating mechanisms. There are no prima facie reasons to assume that paracrine functions are more developed in morphologically primitive SC than in more mature cells. Stem cells are a promising field of research; however, studies of differentiated cells and cell-free products mimicking paracrine effects of cell therapies may be promising as well. Obviously, therapeutic methods with unproven effects should be applied within the framework of sound research shielded from the funding bias.

Keywords: Cardiology, cell therapy, myocardium, stem cells

It is evident for a reviewer of scientific literature that the quality of argumentation in some areas of medical research has deteriorated since the last decades. Publication series of questionable reliability have been continued without making references to the published criticism. Another tendency is that drugs and treatments without proven efficiency are advertized and corresponding products marketed as evidence-based medications. Scientific concepts are sometimes construed for this purpose or existing ones used arbitrarily (1-4). The conclusions of this report are partly based on theoretic considerations. In conditions when it is difficult to distinguish between reliable and unreliable papers, theoretic considerations gain in importance. Some questions are not entirely clear, so that arguments provided here can induce a constructive discussion.

Last time, a large number of publications on stem cells (SC) and cell therapies have emerged, some of them containing attractive terms such as rejuvenation, anti-aging strategy etc. (5-7). Discussed topics include the differentiation of exogenous SC into various cell lineages, replacement of senescent, dysfunctional and damaged cells. Remarkably, assumptions that SC can differentiate into specialized cellular elements have not been confirmed for such a perfect SC as the fertilized ovum. In the "experiment" performed by the nature - extrauterine pregnancy - no differentiation of pluripotent embryonic cells towards surrounding tissues is observed but an embryo and germinal layers are formed. The implantation of embryonic SC can result in a development of teratoma (8, 9). It is known from general pathology that a focal cell proliferation results in the formation of a nodule rather than migration of individual cells into surrounding tissues. For a pathologist, it is difficult to envisage how SC migrate in tissues such as myocardium, liver or cartilage, arrive at the areas where they are supposed to be needed, and engraft in preexisting structures (10, 11), commented in (12). The survival and engraftment rates of SC are regarded to be poor (13).

The migration of SC into ischemic myocardium or infarct zone was reportedly associated with a scar size reduction, cardiomyogenesis and neovascularization (7, 14-17). However, no cardiac SC therapy has been conclusively proven effective (9). Immunohistochemical analyses revealed neither transdifferentiation of mesenchymal SC into cardiomyocytes nor increased vascularization (15). The participation of SC in myocardial regeneration has been questioned and other mechanisms of the therapeutic action assumed e.g. improved vascularization (16, 18). However, the benefit from such vascularization, if it really occurs, is doubtful because ischemia is usually caused by an obstruction of larger epicardial vessels. Accordingly, ischemia can be alleviated by functioning collaterals but not by a locally enhanced microcirculation (19, 20).

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As mentioned above, it is difficult to envisage how SC migrate in tissues. In osteoarthritis, SC would have to move through the dense matrix of hyaline cartilage. If even SC after an intra-articular injection are homing in superficial defects of the joint cartilage, synovial or meniscal surfaces (21), proliferate there and produce extracellular substance, it remains unclear how the smoothness and congruence of joint surfaces is maintained, why the focal cellular proliferation does not result in excrescences crumbling into the articular cavity causing dysfunction and inflammation. Reproducible protocols to induce chondrogenesis by SC are lacking (22). In publications dedicated to the therapy of liver cirrhosis, a differentiation of mesenchymal and other SC to hepatocytes as well as promotion of hepatocyte proliferation is regarded possible (23, 24). "The ability of mesenchymal SC to differentiate into hepatocyte-like cells makes them an ideal alternative method for treating liver fibrosis" (25). However, potential differentiation along the mesodermal lineage e.g. to fibroblasts is not discussed. The fibroblastic differentiation would possibly accelerate the advancement of fibrosis and cirrhosis of the liver or other organs. The theoretical basis for the cirrhosis therapy with SC is hardly comprehensible as hepatocytes are capable of mitosis and can hyper-regenerate in cirrhosis whereas nodules are formed.

The action mode of SC remains incompletely described; alternative mechanisms have been proposed: immunomodulating, paracrine (anti-inflammatory, anti-apoptotic, anti-fibrotic, angiogenic, mitogenic), activation of precursor cells in the microenvironment etc. (7, 26-28). It was hypothesized that SC secrete anti-aging substances (29). However, there are no prima facie reasons to assume that such special functions would be more developed in morphologically primitive SC or partly differentiated progenitor cells than in more differentiated cells. In any case, experiments with mature cells would be less expensive. The same can be said about cell-free products obtained e.g. from cell culture media and mimicking the paracrine action of cell-based therapies. The latter approach would achieve a better dose standardizing than cell implantations whatever is understood under it (30). Meanwhile, doubts regarding efficiency of cell therapies and concerns about their safety are remaining. Allogeneic transplantations carry the risk of infections and immunologic complications (31). Among others, this is a matter of concern when cell therapies are applied for the treatment of diseases with participation of immune mechanisms. Routes of SC administration or "implantation" include transvenous, transendocardial, intracoronary and transepicardial injections (17, 32-34). In this connection, sources of SC used for intracoronary injections e.g. tissues from induced abortions (32) and their purification from potentially immunogenic components are of importance (35). The infusion of autologous bone marrow cells or fractions of the patient's own blood is sometimes named autotransplantation; it is associated with a lower risk than allotransplantation. However, benefits from such procedures are questionable apart from a restoration of the pool of hemopoietic cells after cytotoxic or immunosuppressive treatments (e.g. of hematological malignancies or multiple sclerosis) or similar applications that have been known long since.

Main Points:

- Genetic instability, tumorigenic and immunogenic potential have limited the clinical application of SC.
- There is increasing evidence that a majority of implanted SC do not survive due to the immune rejection and lack of a favorable microenvironment.
- Alternative action mechanisms of SC have been proposed, including paracrine, immunomodulating and trophic. However, there are no reasons to expect more special functions from morphologically primitive SC than from differentiated cells.
- SC are a promising field of research; studies of differentiated cells and cell-free products mimicking paracrine effects of cell-based therapies are promising as well.
- Therapies with unproven effects should be applied within the framework of high-quality research, shielded from bias and to conflicts of interest.

All said, SC seem to be a promising field of research. However, studies of differentiated cells and cell-free products mimicking paracrine effects of cell-based therapies may be promising as well. Unfortunately, the literature is partly biased, exaggerating positive effects, if there are any. Some patients pay for cell therapies; but the experience is partly lost for the science because some conflicted researchers overestimate positive results leaving adverse effects out of attention. One of the objections to prohibitive measures (36, 37) is that the hope is taken from severely ill patients. Obviously, therapeutic methods with unproven effects must be applied within the framework of sound research shielded from the funding bias. Patients participating in such research should be treated free of charge.

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