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Stem cells and cell therapies in cardiology

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Abstract
Last time, a large number of publications on stem cells (SC) and cell therapies have emerged. Discussed topics include the differentiation of exogenous SC into various cell lineages, replacement of senescent, dysfunctional and damaged cells. Some studies claimed that transplanted SC regenerate infarcted rodent hearts. This work was translated to the clinic. However, efficacy in human studies has been nil or ambiguous. It has become clear that exogenous cells were not forming new cardiac tissue. The action mode of SC remains incompletely described; alternative mechanisms have been proposed: immunomodulating, paracrine and anti-aging. However, there are no reasons to assume that special functions would be more developed in SC than in differentiated cells. Allogeneic transplantations carry the risk of infections and immunologic adverse events. In conclusion, SC are a promising field of research. Studies of more differentiated cells and cell-free products mimicking paracrine effects of cell-based therapies are promising as well. Therapeutic methods with unproven effects should be tested within the framework of high quality research shielded from the funding bias.

Keywords: stem cells, allogeneic transplantation, myocardial infarction, heart failure, cardiomyopathy

Introduction

Last time, a large number of publications on stem cells (SC) and cell therapies have emerged, some of them applying such terms as rejuvenation, anti-aging strategy etc.[1-3] 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 [4, 5]. 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 places where they are supposed to be needed, and engraft in preexisting structures [6, 7].

Overall, SC-based therapies of cardiopulmonary diseases are still at their preliminary stage [8]. The poor engraftment and survival of implanted cells is a recognized challenge [9, 10]. Since the early 2000s, several studies claimed that transplants of bone-marrow or other SC can regenerate the infarcted rodent heart. This work was translated to the clinic. However, efficacy in human studies has been nil or ambiguous. It has become clear that donor cells were not forming new cardiac tissue[11]. As for the adipose-derived cell therapy with cardiac or systemic administration, there have been adverse events and no clear clinical evidence for the efficacy [12]. The action mode of SC, if any, 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 [3, 13-15] It was hypothesized that SC secrete anti-aging substances[16]. However, there are no prima facie reasons to assume that special functions would be more developed in morphologically primitive SC or partly differentiated progenitors than in more differentiated cells. Note that the biological mission of SC is mitosis rather than secrtion of specific cytokines. In any case, experiments with mature cells or cell-free products would be less expensive. The cell-free substances mimicking paracrine effects of cell-based therapies can be obtained e.g. from cell culture media. The latter approach would achieve a better dose standardizing than cell implantations whatever is understood by it [17].

Allogeneic transplantations carry the risk of infections and immunologic adverse events [18]. Among others, this is a matter of concern when cell therapies are applied for the treatment of diseases with participation of immune mechanisms in the pathogenesis such as cardiomyopathy. In cardiology, routes of SC "implantation" include transvenous, transendocardial, intracoronary and transepicardial injections [19, 20-22]. In this connection, sources of the cell material for intracoronary injections e.g. abortion specimens and its purification from immunogenic components are of importance [20]. The infusion of autologous bone marrow cells or fractions of the patient's own blood is sometimes named auto transplantation; it is associated with a lower risk than the all transplantation. 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) that have been applied long since. Numerous cell therapies have been patented; just one recent example: cells collected from human placentas and umbilical cords were injected into acupuncture points as a "method of treatment of ischemic angiopathy of lower extremity vessels [23].

Conclusion

All said, 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. Cell therapies with scant evidence of efficacy should not be applied in human heart diseases [11]. Continuing to pour money into ineffective forms of cell therapy diverts funding from approaches that merit further investigation [11]. Some patients pay for cell therapies; but the valuable experience is partly lost for the science because conflicted researchers tend to overestimate positive results (if there are any) leaving adverse effects out of attention. One of the objections to prohibitive measures [24, 25] is that the hope is taken from severely ill patients. Obviously, therapeutic methods with unproven effects must be tested within the framework of high quality research shielded from the funding bias. Patients participating in such research should be treated free of charge. As for animal experiments, they must be also performed by integer researchers not influenced by conflicts of interest. Low quality studies increase the risk of bias i.e. misrepresentation of reality [12]. The deception is objectionable on the grounds that it limits autonomy and breaches trust; these grounds possibly do not apply to placebos when they are prescribed within appropriate ethical limits [26], although it can be problematic both on the professional and ethical levels [27]. In other words, placebo therapy with misinformation of a patient can be beneficial and ethically justifiable [28], but it is not a sufficient reason to publish biased information. In conclusion, the following statement should be agreed with: "…doubts will further raise the question if patients should spend their money for useless drug with no clear mechanism of action which shows no or little evidence of its efficiency" [29].

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