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## Stem cells - a new rescue in cardiology?

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### ABSTRACT

In recent years stem cells have become the object of curiosity for many researchers and clinicians. Interest in the use of these cells is an effect of their specific properties. Their great potential for self-renewal as well as the ability to differentiate into specific cell types is particularly interesting. These unique features allow us to think about stem cells as a possible therapeutic solution in the treatment of damaged tissues. The tissue that is particularly vulnerable to damage is heart muscle, which consists of cardiomyocytes. These cells are extremely vulnerable to lack of the oxygen, what can be observed in the case of temporary cardiac ischemia, e.g. during physical exertion or in stressful situations, which initially manifests as stable angina. Prolonged ischemia and consequent hypoxia of cardiomyocytes lead to their death what is manifested as myocardial infarction. An extensive area of post-infarction necrosis impairs heart functioning as a blood pumping organ what leads to its failure. Researchers are still searching for a therapy that would replace large areas of dead cardiomyocytes with new cells, and thus potentially minimize the negative effects of myocardial necrosis and postpone the impairment of its function. Due to their properties, it seems a good idea to introduce stem cells as a method of treatment, hence many studies are conducted to demonstrate the effectiveness of these cells in the treatment of cardiac patients. This paper presents a literature review of stem cell applications in the aforementioned cardiac diseases, taking into account the obtained results.

**Keywords:** stem cells, myocardial infarction, heart failure, stable angina

## **1. INTRODUCTION**

Cardiovascular system disorders are the most common cause of death in the world. According to data from the American Heart Association, in 2013, 17.3 million people died due to cardiovascular diseases. This accounted for 31,5% of all deaths in the world, of which 8.2 million were caused by ischemic heart disease and 6.5 million by stroke, which together accounted for 85% of deaths from cardiovascular system diseases.

Currently, cardiac patients are treated with a wide number of methods, including pharmacological therapy, cardiac resynchronization therapy, or the possibility of cardioverter-defibrillator implantation. However, in such conditions as a history of myocardial infarction, which leads to cardiomyocyte necrosis or heart failure leading to serious dysfunction of this organ, the above-mentioned therapies are insufficient to prevent progression and serious consequences. In patients with end-stage heart failure, transplantation is the only effective method. Unfortunately, many patients will not survive until surgery because of a much larger number of recipients than the heart donors. Therefore, new and effective therapeutic methods are still being investigated for chronic cardiovascular diseases. [1]

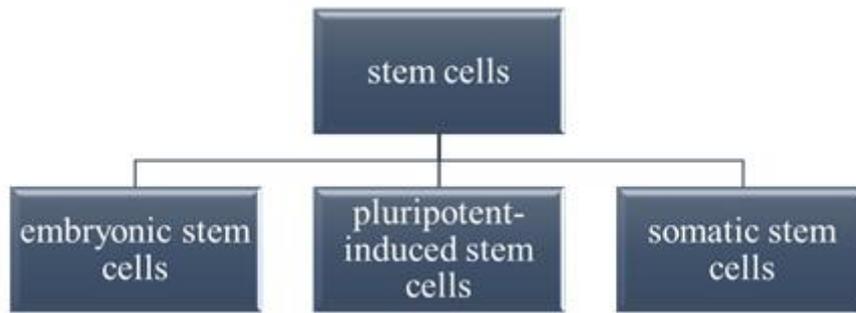
## **2. STEM CELLS**

The difference between stem cells and other body cells closes in their three properties: self-renewal potential, differentiation into specialized cells and the ability to transform into precursor cells. Due to their plasticity, these cells can, under appropriate conditions, transform from a non-specialized cell into a cell that has characteristic properties of specific tissue. The ability of asymmetric and symmetric cell division gives the possibility of both self-renewal of undifferentiated stem cell and a generation of cell that performs characteristic organ functions. [2]

The types of stem cells used in medicine are embryonic stem cells (ESC), pluripotent-induced stem cells (iPSC) and somatic stem cells (MSC). The first two types are particularly interesting due to their pluripotent effect [2].

ESCs, as the only type of stem cells, have a totipotential character and are nothing else than blastomeres of a dividing zygote, therefore they can differentiate into any kind of tissue. The problematic aspect of usage of these cells, in addition to the immunological specificity, is also the ethical background, because it involves the destruction of the embryo from which we collect the material. In addition, there is also a probability of neoplastic transformation because of their unlimited ability to divide [3].

Somatic stem cells are responsible for the growth and regeneration of damaged tissues. Their presence was demonstrated, among others in the bone marrow, umbilical cord blood, liver, skin and brain. They have the ability to migrate to the area of damage and transform into another tissue, which means they give the possibility of autograft for the patient without the necessity of preparation with immunosuppressive drugs [2].



**Figure 1.** Classification of stem cells.

Induced pluripotential stem cells are cultured by introducing a vector into the murine blastomeres that carry the OCT  $\frac{3}{4}$ , Sox2, c-Myc Klf4 genes, which reprograms the cell nucleus. In the first stage, thanks to the c-Myc and Klf4 genes, the barrier against anti-oncogenes is exceeded, in the second, by the presence of OCT  $\frac{3}{4}$  and Sox2 genes, the cell acquires pluripotent features. The c-Myc factor works by induction of global acetylation of histones what enables the binding of OCT  $\frac{3}{4}$ , Sox2 factors [4].

Finally, the mature cell transform into embryonic, able to differentiate in any direction [2]. Analogously to embryonic cells, their uncontrolled division is associated with the risk of carcinogenesis.

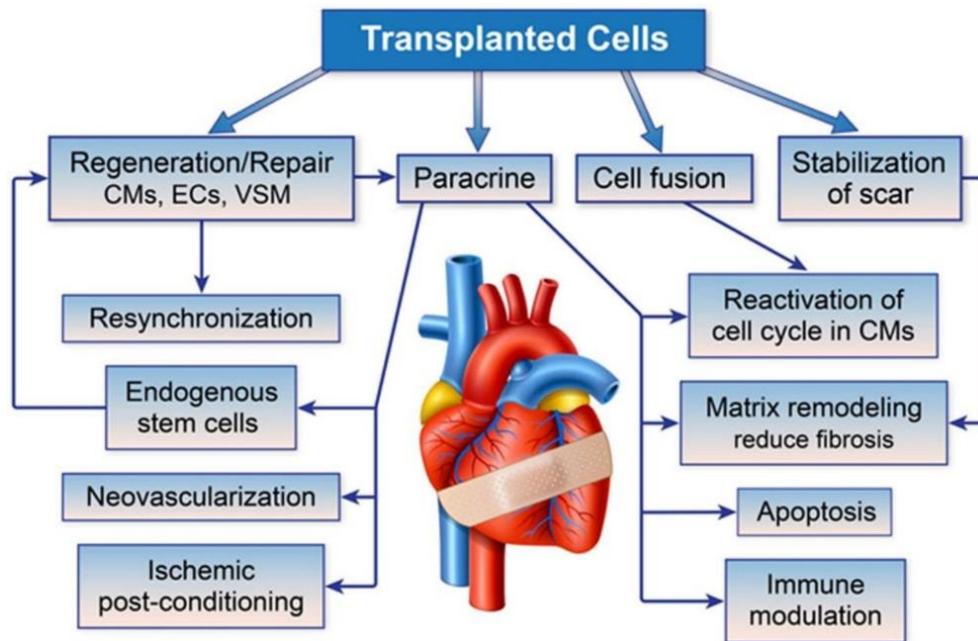
The therapeutic potential of stem cells largely depends on the place and time of their collection, because it decreases with the age of the organism [2]. The suitability of a cell is related to its ability to proliferate and differentiate. To maintain the ability of self-renewal, it is necessary to activate the Notch protein, Wnt and Shh pathways, which are closely controlling these processes [3].

In cardiology, the greatest hope is connected with the therapy with pluripotent stem cells derived from the bone marrow (both hematopoietic and mesenchymal lineage) and iPSC [3, 9].

The sources of mesenchymal stem cells, in addition to bone marrow, are also adipose tissue, umbilical cord blood and amniotic fluid. The process of stem cells isolation takes several stages, using the difference in density, adherence to plastic and trypsinization. Their phenotypic characteristic is carried out with monoclonal antibodies, and their low immunogenic and immunomodulating properties contribute to the frequent use of mesenchymal cells in research on stem cell therapies. [5, 6]

Heart regeneration through stem cell implantation involves the creation of biological cardiac pacemakers, electrical stabilization, and the renewal of post-infarction myocardium by multiplying the number of functional cardiomyocytes. Their paracrine capacity, which has beneficial effects on damaged tissues should also be considered [4, 25]. Mesenchymal stem cells secrete interleukin 6, fibroblast growth factor, hepatocyte growth factor, PAF and VEGF, which help to repair tissues. In addition, by secretion of cytokines, they stimulate already present myocardial stem cells for the division, as well as they protect the heart by inhibiting the secretion of proinflammatory cytokines [6, 8]. Embryonic stem cells have a different range of secreted substances. The most important of them are HASF (hypoxic-induced act regulated stem cell factor), angiopoietin 1 and 2, endothelial growth factor and metalloprotease inhibitors involved in remodeling of extracellular matrix [7].

The application of stem cells to damaged myocardium can be carried out in several ways. The least effective is their intravenous administration. The coronary pathway involves administering the cell suspension directly to the infarct-related artery, but the effectiveness of the method decreases with the time that has elapsed since the incident of acute myocardial ischemia. More invasive method requiring thoracic surgery is a direct injection of stem cell into endo- and epicardium [3, 25].



**Figure 2.** Beneficial effects of stem cells therapy [25].

## 2. 1. Stem cells in myocardial infraction

Myocardial infarction is the clinical condition during which closing of the coronary artery leads to ischemia in the area of the heart muscle supplied by this artery. Its effect is the formation of necrosis, in which the cardiomyocytes cease to fulfill their most important function, they stop shrinking. These cells do not have any regenerative abilities, which is a significant problem for the prognosis of patients after myocardial infarction. This state consequently leads to lowering the ejection fraction of the heart and its failure. [10]

Therefore, researchers are still searching for therapies which could allow to reduce the size of the dead region of the myocardium, and thus would enable a longer preservation of normal heart functioning. [11, 12] For this purpose, many studies are carried out using several therapies including stem cells. A meta-analysis of forty randomized controlled trials conducted between 1990 and 2016 was performed, which included a total of 1,927 patients. The criteria for study inclusion in the analysis were: duration of follow-up  $\geq 3$  months, patients diagnosed with myocardial infarction divided into two groups, English or Chinese language of publication. In the first of these - the experimental group underwent percutaneous coronary intervention and received autologous bone marrow stem cells, while the second group - control, underwent a standard regimen. The studies were analyzed towards differences in left ventricular ejection

fraction ( $\Delta$ LVEF) in patients in both groups. In most cases, it was shown that patients who received stem cell transplants showed improvement in LVEF. In addition, a correlation between the number of administered cells and LVEF was also observed. However, the results of the nine studies from this meta-analysis showed no improvement or worsening of LVEF in patients undergoing stem cell therapy compared to patients in the control group. The authors of the meta-analysis found that the observation period of the majority of included studies was shorter than 3 years, which means that long-term results of the investigated parameters are missing, therefore further studies are needed to evaluate the exact effect of stem cells in patients after the heart attack [13].

## **2. 2. Stem cells in the treatment of heart failure and angina pectoris**

Heart failure is a frequent, irreversible and fatal disease that causes a significant degree of disability. Currently, its treatment, without counting a small percentage of heart transplants, consists only of attempts of controlling symptoms and prevention of further myocardium damage.

At the turn of the 20th and 21st centuries, a concept for implementing heart regenerative therapy with stem cells was developed. The first reports on the potential benefits of such a procedure come from the work of Taylor et al. (1998) who noticed an improvement in the heart work of rabbits after autologous implantation of skeletal muscle myoblasts into areas affected by infarction [14]. Since then, many authors have been working on this topic, in order to find a way to reverse myocardial damage and improve the prognosis of patients. In the last ten years, many types of stem cells have been used for this purpose, in addition to previously mentioned skeletal muscle-derived cells, also cells derived from the bone marrow, adipose tissue, blood or the heart itself. The mechanism of their therapeutic action on the myocardium is not fully understood and it is suspected that it may involve the activation of progenitor cells present in the heart, stem cell differentiation into cardiomyocytes, smooth muscle cells of coronary artery walls, endothelial cells, remodeling of extracellular matrix or inhibition of apoptosis. Despite promising results of some studies, including increased ejection fraction, reduction of the myocardial necrosis area, increased distance passed by the patient in the 6-minute walk test, or reduction of the severity of heart failure symptoms in the NYHA classification, they are mainly derived from non-randomized studies. In addition, side effects of therapies consisting mainly of ventricular arrhythmias and sudden cardiac death (especially in the treatment with skeletal muscle stem cells) have been observed. When using bone marrow stem cell therapy, the number of observed complications is significantly lower, however, the majority of randomized studies show no significant benefits in the group of patients undergoing this therapy compared to the placebo control group [15].

In the largest randomized research conducted so far in patients with ischemic heart disease (involving 271 patients), CHART-1, in which isolated mesenchymal stem cells of their bone marrow were used despite no improvement in mortality, exacerbations of heart failure, the final left ventricular volume (LVEDV) and left ventricular ejection fraction (LVEF), a smaller number of sudden cardiac deaths and a significant improvement in cardiac function parameters among patients with baseline LVEDV in the range of 200-370ml were observed [16]. These observations give hope for the potential benefits of stem cell treatment in at least some groups of patients with heart failure and they should lead to further randomized trials with this therapy.

The use of stem cells is also considered in angina pectoris therapy, in which there are ischemic, but still vital areas of the myocardium. Such therapy would be particularly useful for

refractory angina when revascularization of ischemic areas is impossible. In the Polish, randomized REGENT-VSEL study in the study group, CD133+ marrow stem cells were administered to the NOGA electromechanical mapping system identified by vital areas of the left ventricular muscle. In the control group, sodium chloride was used for this purpose. After the observation period, no differences were observed in the quality of life, myocardial perfusion and severity of CCS symptoms between the examined groups of patients [17].

### **2. 3. Adverse effects of stem cell therapy**

The use of stem cells in cardiology creates new treatment options for both acute and chronic diseases affecting the cardiovascular system, but like all other methods of treatment, it has several side effects. Stem cells, as already mentioned, can be obtained in many ways - one of them is the induction of cell reprogramming to restore their pluripotency. Already at this stage, errors associated with genomic instability and down-regulation of genes inhibiting carcinogenesis can occur. [18]

Frequent problems also include the limited number of cell divisions used for transplantation and their inadequate differentiation into cardiomyocytes, which does not allow them to act as efficient myocardial cells. [19] However, the main problem with stem cell implantation is the failure of the procedure itself. Immediately after administration (usually to the coronary arteries or directly to the myocardium) they can be irreversibly damaged. Its mechanism can be connected with their inadequate nutrition and the production of free oxygen radicals. Stem cells often are unable to create gap junctions with surrounding cardiomyocytes, which makes their implantation impossible. [12, 20]

Implantation may also be unsuccessful if the cells are delivered to the coronary artery, which is significantly narrowed by atherosclerotic plaques and the target part of the myocardium is not adequately supplied with blood [20]. In addition, any implantation of cells (even autologous!) can cause immunological and inflammatory reactions that prevent their proper implantation. [18] Sometimes after implantation, cells may not achieve full metabolic efficiency and electrical integrity with the rest of the myocardium. Stem cells obtained from the bone marrow do not have any specific markers on the surface that would allow their identification after implantation into the heart, which makes it difficult to properly monitor the progress of therapy. [22]

Successful cell implantation also has various side effects including cardiac arrhythmias - most often atrial fibrillation, due to the asynchrony of the implanted cells with the electrical activity of other cardiomyocytes. [23] Teratocarcinomas can also develop, most frequently after intradermal and subcutaneous as well as endovascular injections with undifferentiated cells whereas, from injected cells that differentiate into mature cardiomyocytes, primary malignant tumors, e.g. rhabdomyosarcoma, may arise. [18, 24]

Cases of calcification and ossification of the damaged parts of the myocardium after injection of stem cells have also been described. [24]

### **3. CONCLUSIONS**

Stem cells due to their self-renewal and plasticity properties are undoubtedly an interesting and promising therapeutic challenge in the treatment of chronic cardiovascular system diseases. The studies carried out so far on patients suffering from angina pectoris, heart

failure and after myocardial infarction are not entirely clear. Some of the obtained results indicate the benefits of stem cell therapy, however, many of them show that the implantation of these cells in cardiac patients was not connected with the clinical condition improvement. Additionally, also a risk of side effects associated with their implantation should be considered. Therefore, further research using stem cells is needed that will allow long-term patients' observation and accurate assessment of the effectiveness of this therapy.

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