

# Stem cells and heart: an open future or a mirage?

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## Proceedings

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*Stem cells: present and future*

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## Abstract

Stem cells (SC) look like to be the possible solution to a number of human pathologies, including those involving the heart.

In fact, some studies based on animal models suggest that SC can be used to repair the damaged cardiac tissue, such as in case of myocardial infarction. In fact it has been demonstrated that it would be possible to produce a quantity of SC sufficient to repair an animal heart having physiology and dimensions as the human heart.

The aim of this short review is to examine the different subtypes of SC potentially involved in the heart repair (autologous and heterologous) processes as well as the serious concerns that have still to be overcome before considering SC a sure therapy for the heart diseases: rejections, oncogenesis due to SC high proliferative activity, difficult in ruling their differentiation, massive SC death when introducing them in an ischemic environment, ethical problems when SC are derived from embryos.

## Keywords

Stem cells, heart failure, myocardial infarction, regeneration.

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## Background

Stem cells (SC) look like to be the possible solution to a number of human pathologies, including those involving the heart. For example, cellular therapy has emerged as a potentially novel treatment for severe ischemic heart disease, and there is increasing evidence that SC transplantation may improve the perfusion and contractile function of ischemic myocardium.

In fact, some recent studies suggest that SC can be used even to repair the damaged cardiac tissue in case of myocardial infarction. The latter is generally induced by the interruption of the blood flow through the coronary arteries, which are the vessels that deliver the oxygen-rich blood to the myocardium. The consequence is a weakened heart with an impaired myocardial contractility [1].

In an animal model involving a group of monkeys suffering from myocardial infarction for more than 90 minutes, about a billion of SC have been inserted in the heart two weeks later, in order to study their action [2]. It has been observed that SC had the ability to infiltrate the damaged cardiac tissue, thus progressively transforming themselves in cardiac fibers.

After three months from the SC injection, these new fibers have been able to beat synchronously with the original cardiac muscle cells, being part of a repaired heart.

The side effects have been few: only some extrasystolic beats have been registered, which disappeared in two or three weeks. For the first time it has been demonstrated that it has been possible to produce a quantity of SC sufficient to repair an animal heart having physiology and dimensions as the human heart. The authors of this research aimed at repairing the cardiac muscle of men affected by myocardial infarction within the next years [2].

## Different kinds of stem cells useful for the heart

The SC are undifferentiated biological cells that can differentiate into specialized cells and can divide (through mitosis) to produce more SC.

There are three known accessible sources of autologous adult SC in humans:

1. bone marrow;
2. adipose tissue;
3. blood.

SC can also be taken from umbilical cord blood just after birth.

Endothelial SC are one of subtypes of SC found in bone marrow. However they can be isolated also in umbilical cord blood as well as in peripheral blood. They are identified through the analysis of some surface proteins and thus subdivided into *early*, *late*, and *mature* endothelial SC (Cd133+ Cd34+; Cd133- Cd34+; VWf+, respectively). They have a phenotype and a function similar to those of angioblasts. After i.v. injection, these SC are able to reach the ischemic cardiac area and promote the development of new vessels even in the surroundings. The consequence is a reduction in collagen deposition as well as in the cardiomyocytes apoptosis, which in turn lead to increased ventricular contractility. It is important to underline that endothelial SC are not able to differentiate in cardiac muscle cells [3].

On the contrary, specific SC from umbilical cord blood have the capacity to differentiate into specialized cell types, cardiomyocytes included [4].

Induced pluripotent stem cells (also known as IPS cells) are a type of pluripotent SC that can be generated directly from adult cells. In fact, the introduction of four specific genes (Oct4; Klf4; Sox2; c-Myc) encoding transcription factors could convert adult cells into IPS [5]. IPS cells can differentiate towards any cell-lineage, including cardiac cells.

They hold great promise in the field of regenerative medicine and have a cardiogenic potential similar to that of embryonic SC. IPS derived cardiomyocytes have the typical characteristics of cardiac muscle cells, that are spontaneous electrical activity, contractility, and presence of ionic channels.

Depending on the applied technique, the conversion of adult cells into IPS cells may induce significant risks that could limit their use in humans. For example, the expression of oncogenes (cancer-inducing genes) may potentially be

triggered. However, in the past years it has been discovered a laboratory method that could remove oncogenes after the induction of pluripotency, thereby increasing the potential use of IPS cells in human diseases [6].

### Reduced stem cells survival in the ischemic environment

SC may have a poor engraftment and survival after transplantation in an ischemic heart. This may be due to different factors, such as inflammatory cells, mechanical damage, ischemia/riperfusion damage with subsequent inflammation and oxidative stress. The SC death is induced by apoptosis [7].

Some strategies have been proposed in order to avoid this problem. As a general rule, they are based on the attempt to induce the so called ischemic preconditioning phenomenon. The latter is an intrinsic cardiac autoprotective mechanism whereby repeated short episodes of ischemia protect the myocardium against a subsequent ischaemic insult. It was first described about thirty years ago by Murry et al. As pioneer in this field, this research group exposed anesthetized open-chest dogs to a four period of 5 minute coronary artery occlusions followed by a 5 minute period of reperfusion before the onset of a 40 minute sustained occlusion of the coronary artery. The control group of animals had no such period of ischemic preconditioning and had much larger infarct sizes compared with the dogs in the study [8]. The main molecular pathways involved in the ischemic preconditioning acts through the regulation of hypoxia-inducible factor (HIF) 1 $\alpha$  [9]. The ischemic preconditioning can be induced in other ways as well (i.e. potassium channel activator diazoxide administration; gene encoding for interleuchin-1 manipulation; prevention of the immune reaction through the administration of humanized anti-CD154 antibody before and after SC transplant; administration of VEGFR, insulin-like factor, and fibroblasts growth factors; thermic shock) [9].

### Stem cells different ways of administration

The main ways are three:

1. transc coronary cell injection;
2. intracoronary cell infusion;
3. direct intramyocardial cell injection (transepicardial or transendocardial).

The transc coronary cell injection is a simple but not well efficient way to administer SC in the heart. It is based on the fact that high levels of circulating cytokines and growth factors are able to attract the SC in the ischemic area. However, many SC have been lost in other areas owing to the hepatic filtration.

The intracoronary cell infusion allows the release of high SC concentrations in the ischemic area.

The best method for intracoronary administration of SC is to stop coronary flow through a balloon during SC infusion, in order to prolong the contact between the SC and the vascular wall, enhance adhesion, and promote extravasation of the SC into the interstitial space. However, the temporary occlusion of a coronary artery is not without serious risks of coronary dissection, distal embolization, and vasospasm.

In the direct intramyocardial cell injection, SC injection can be conducted by multiple *transepicardial* punctures during an aorto-coronary by pass. The main advantage of this approach is the precise visualization of the myocardial area where the SC need to be inoculated, while the main disadvantage is that this method is too invasive. Based on these premises, the less invasive *transendocardial* approach is usually preferred. SC have been delivered in the necrotic areas – previously detected by Single Photon Emission Computed Tomography (SPECT), by minimally invasive endomyocardial injections. One of the benefit of the transendocardial approach is that it can be performed in patients suffering from chronic ischemic heart disease, where the presence of necrotic areas constitute an obstacle to the diffusion of the SC inoculated with the other techniques. Recently, the SC transplant in the heart through bioscaffolds has been proposed as well [10].

### Cardiac autoregenerative potential

Recent reports indicate that the adult mammalian heart is capable of limited, but measurable, cardiomyocyte turnover, which is more evident during the neonatal life and declines throughout life. The origin of the newly developed cardiomyocytes is not completely known, even it has been suggested that they may be derived from an unidentified cardiac progenitor population, with unknown localization (mainly in the hypoxic regions?). A number of resident cardiac progenitor

cells have been identified in the heart based on the expression of surface markers such as c-kit, Scal-1 and Isl-1.

Many of the above stated cardiac progenitor cells demonstrate capacity for self-renewal and can differentiate into cardiomyocytes and vascular lineages *in vitro*.

Meis1 expression pattern in the postnatal heart is probably involved in the cardiac autoregenerative potential. In fact, cardiomyocyte specific deletion of Meis1 in the cardiomyocytes led to their massive proliferation. More importantly, inducible Meis1 knockdown in the adult heart is associated with reactivation of cardiomyocyte cell cycle [11].

### Today limits of stem cells and open future

At this time, several serious concerns have still to be overcome before considering SC a sure therapy for the heart diseases: rejections, oncogenesis due to their high proliferative activity, difficult in ruling their differentiation, possible massive SC death when introducing them in an ischemic environment, ethical problems when SC are derived from embryos.

Some of these problems might be solved with a more in depth knowledge of the mechanisms involving the SC differentiation and therapeutic action.

In this respect the metabolomics, a new and promising laboratory technique which allows the systematic study of the complete set of metabolites in a biological sample, appears to be able to play a pivotal role in the identification of a possible future and more extensive SC involvement in the cardiovascular system repair [12, 13].

### Declaration of interest

The Authors declare that there is no conflict of interest.

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