Review article

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THE ROLE OF MESENCHYMAL STEM CELLS IN THE THERAPY OF MYOCARDIAL INFARCTION

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Mesenchymal stem cells (MSCs) are multipotent stromal cells that can differentiate into osteoblasts, chondrocytes, adipocytes. During the early 21st century, in vivo studies demonstrated that human MSCs can transdifferentiate into endoderm-derived cells and cardiomyocyte phenotype. Without blood to supply cardiomyocytes (CMs), as in myocardial infarction, the loss of functional CMs progresses as an imbrication of necrosis, apoptosis and autophagy. Besides progressing through different stages of inflammation and healing, the dynamic microenvironment in the infarcted tissue also expresses cardiac cytokines that promote stem cell migration and homing. Given the uncertainty of myocardial salvage, dictated by the degree of necrosis from the sentinel event, it soon became clear that in order to change the long term outcomes of acute myocardial infarction, it is needed to search for a therapy that takes the time to presentation out of the equation. A possible solution to that dilemma appeared in the form of targeted stem cell therapy.

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Introduction

Mesenchymal stem cells (MSCs) are adult, multipotent cells that have the ability to differentiate into tissues of mesodermal origin. Also, they are self-renewable, fibroblast-like cells (1, 2, 3).

First knowledges about stem cells are given by Friedenstein et al. in the 1970s (4). They showed that the bone marrow contains a population of hematopoietic stem cells (HSCs) and an infrequent population known as mesenchymal stromal cells and displayed the capacity of MSCs to differentiate into mesoderm-derived tissue and their significance in regulating hematopoiesis (4, 5). In the 1980s, it was established that MSCs can differentiate into osteoblasts, chondrocytes, adipocytes (6, 7), and into a myogenic phenotype in the 1990s (8). Pittenger et al. demonstrated that adult human MSCs can be expanded to colonies while retaining their multilineage potential (9). In later years, *in vivo* studies demonstrated that human MSCs transdifferentiate into endoderm-derived cells and cardiomyocytes (10, 11) dna *in vitro* coculturing of ventricular myocytes with MSCs induced transdifferentiation into a cardiomyocyte phenotype (12), and discovered their immunomodulatory functions (13). MSCs also suppress T-lymphocyte proliferation, so can be used for allogeneic transplantation and as a potential immunomodulatory therapy (13) (Figure 1).

MSCs are found in the bone marrow, amniotic membrane, synovial fluid, cord blood, adipose tissue, Wharton's jelly, placenta, umbilical vein, amniotic fluid, skeletal muscles, liver and, cord or peripheral blood (14, 15). This wide variety of origins, methodologies, and acronyms prompted standardization in 2005 by the International Society for Cellular Therapy, which set the minimum requirements for MSC definition (16). The minimum criteria for MSCs included plastic adherence, *in vitro* trilineage differentiation to osteoblasts, adipocytes and chondroblasts, cell surface expression of CD105 (endoglin, SH2), CD73 (ecto-5'-nucleotidase, SH3/4), and CD90 (Thy1) and the absence of CD45, CD34, CD14 or CD11b, CD79α or CD19 and HLA-DR (17).

MSCs have high expansion potential in culture, giving the large numbers of cells within a short period of time, which is of importance in transplant medicine (18, 19, 20). MSCs are characteristic by genetic stability, compatibility with tissue engineering principles, reproducibility of features between different bone marrow isolates, their potential to

trigger regeneration in various fundamental tissues including the myocardium and neovascularization, their ability to home to the damaged tissue or inflammatory sites, and their immunoregulatory properties and so their use as an allogenic treatment (18, 19, 20). It has been shown that MSC transplantation may give benefits in various diseases (21), and one of those diseases in which their ability has been researched a lot was heart attack (MI).

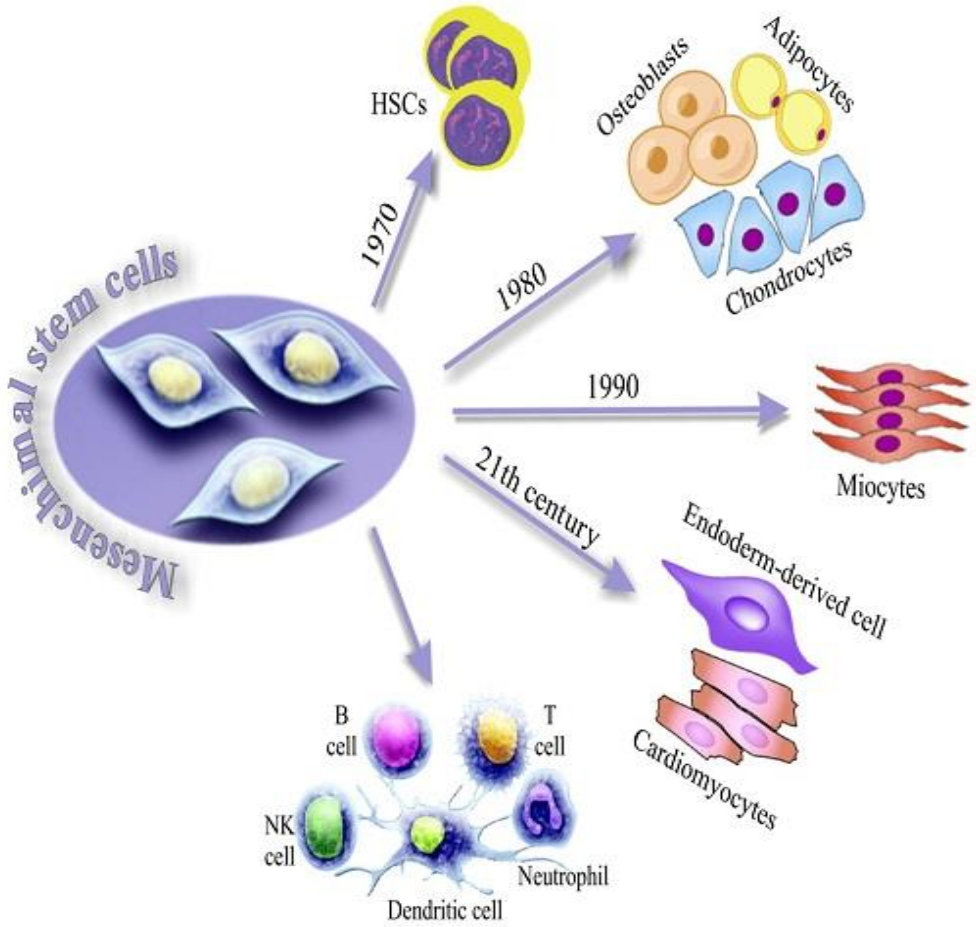

Figure 1. Roles of MSCs

Myocardial infarction and homing endogenous MSCs

Myocardial infarction (MI) is a consequence of the irreversible damage of heart muscle cells, when prolonged ischemia exceeds a critical threshold and overwhelms myocardial cellular repair mechanisms. On this way, functional cardiomyocytes (CMs) pass through processes of necrosis, apoptosis, and autophagy (22, 23).

Besides progressing through different stages of inflammation and healing, the dynamic microenvironment in the infarcted tissue also expresses cardiac cytokines that promote stem cell migration and homing (24).

Stem cells, whether endogenous or exogenous, may reach to the myocardial inflammation, as it has been shown in many studies (25). Also, it has been shown that MSCs homing depends on the nature of MSCs and on the time of their application (25) (Figure 2).

Homing depends on the chemokine receptor CXCR4 which is present on a subpopulation of MSCs and its binding partner, that is, stromal-derived factor-1 CXCL12 (25). Freshly isolated BM MSCs and cultured MSCs also express CCR1, CCR4, CCR7, CCR10, CCR9, CXCR5, and CXCR6 which also participate in MSC migration (25). Adipose-derived MSC-like cells express integrins, cell surface molecules that participate in migration of variety of cells, while neutralizing antibodies against integrins (integrin-beta1 integrin, but not integrin-alpha 4 which is involved in MSC migration) inhibit MSC homing to infracted myocardium (25).

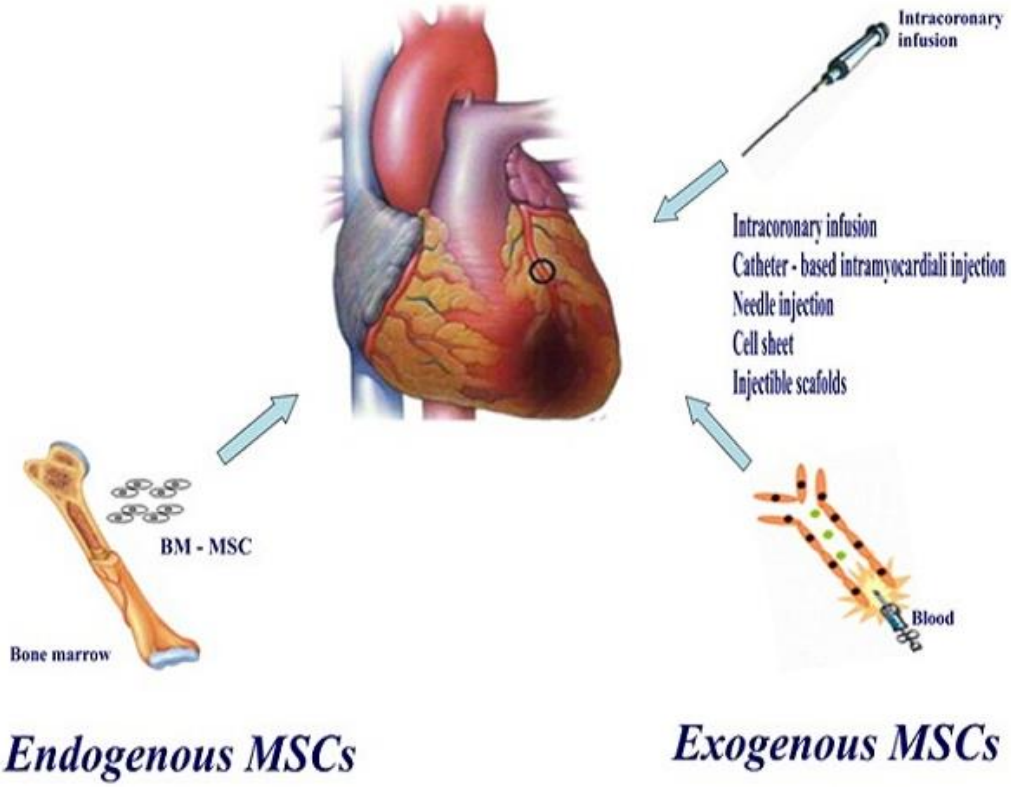

Figure 2. MSCs therapy in myocardial infarction

MSCs transplanting to the post-infarct myocardium

Transplanting stem cells to the post-infarct myocardium augments the cytokine effect to attract endogenous stem cells, via their paracrine mechanisms (anti-inflammatory and immunomodulatory mechanisms) and on that way modulate the regenerative environment (26). MSCs secrete an array of growth factors and anti-inflammatory proteins in response to inflammatory molecules such as interleukin-1 (IL-1), IL-2, IL-12, tumor necrosis factor-α (TNF-α) and interferon-gamma (INF-γ). These factors have feedback mechanisms among the many types of immune cells (27). The key immunomodulatory cytokines include prostaglandin 2, TGF-β1, HGF, SDF-1, nitrous oxide, indoleamine 2,3-dioxygenase, IL-4, IL-6, IL-10, IL-1 receptor antagonist and soluble tumor necrosis factor-α receptor (27). MSCs prevent proliferation and function of many inflammatory immune cells, including T cells, natural killer cells, B cells, monocytes, macrophages and dendritic cells (27).

After the transplantation to the post-infarcted myocardium, MSCs decrease protein production and gene expression of inflammation cytokines TNF-α, IL-1β and IL-6, inhibit deposition of type I and III collagen and gene and protein expression of MMP-1 and TIMP-1 (27). So MSCs preventing myocardial remodeling after MI, due to their capability to attenuate LV cavitary dilation and transmural infarct thinning, and to increase EF, FS, LVESP and dp/dtmax, decrease LVDd, LVEDV, LVEDP (27). MSCs also have the cardiac protective effect in ischemic heart disease thanks to their anti-inflammatory role (28).

Endogenous stem cells, beside the paracrine signaling effects, have the potential to differentiate into functional myocardium (24). Together, the delivery and differentiation of stem cells replenish the lost cardiomyocytes from MI and provide increased vascularity in the post-injury zone to prevent further ischemic tissue damage (29).

MSCs as novel therapeutics

In response to acute MI, MSCs, as novel therapeutics, can be developed to promote CMs survival and improve cardiac function after MI (30, 31). Actually, the gold standard for resolving acute MI is percutaneous coronary intervention (PCI) (32). The aim of any medical or surgical therapy is to establish revascularization and limit the degree of myocardial injury, so targeted stem cell therapy is a possible solution (33, 34).

In comparison with the other cell types, MSC therapy can be promising option in AMI treatment (11, 35). The border zone between necrotic myocardium and viable myocardium is part of interest, and depends on the reaction of viable myocardium to the

area of infarct (20). It is stem cells home to the injured myocardium, in order to produce a therapeutic response. They adhere to myocardium and transmigrate through the endothelium, invade the interstitium and at the end engraft the damaged myocardium (36).

Goals of stem cell therapy

The main goal of cell-based therapies for cardiac diseases is to stop damaging of myocardial tissue and establish its revascularization by accelerating the normal healing process, improving vascularization, inhibiting apoptosis and potentially regenerating cardiac muscle (37, 38). MSC therapy has found application in myocardial repair whether in ischemic heart diseases or in heart failure patients (20).

Limitation and improvements of cell-based therapy

Because of the low retention of cardiac stem cells regardless of the delivery method used, it is needed to improve their engraftment and differentiation in the future.

There are several limitations based on most previous clinical trials of cell-based therapies: low engraftment of BMCs, poor survival of transplanted cells in ischemic tissue, failure of adult stem cells to differentiate efficiently into mature and functional cardiomyocytes, inadequate recruitment of circulating or resident cardiac stem cells, anomalous electromechanical coupling between the transplanted cells or between the transplanted and host cells with consequent arrhythmias (39).

There exist some difficulties that interfere with the evaluation of the effect of cell-based therapy, like the use of LVEF for assessing the effects of cell therapy, incorrect target population of not very sick patients with baseline LVEF 50% and existence of alternative therapeutic strategies like PCI and standard medicament treatment (39).

Homing of stem cells can be improved by using extracorporeal shockwaves of the target organ or tissue. Hydrogels, cell sheets, prefabricated matrices, microspheres and injectable nanomatrix have been used for improving retention of transplanted cells (39). Also, correction of environment conditions can help in cell retention as well as using genetic engineering tools, including overexpression of pro-survival genes or by transplanting the cells together with pro-survival or pro-angiogenic factors or transplantation of preconditioned cells that suppress inflammatory factors and immune responses, and promoted heart function (39).

Questions remain about whether adult stem cells in the heart truly undergo functional and electrical integration and whether this may have hypocontractile and proarrhythmic consequences.

Conclusion

Many preclinical and clinical studies performed on animal and human models have showed that MSC therapy is safe and effective therapy for cardiac regeneration, although their healing mechanism is not precisely defined. MSCs do not appear to be rejected by the immune system, have great growing potential and the ability to enhance tissue repair. Understanding adult stem cells such as MSCs is to provide further development of this field and eventual use of other stem cells in the treatment of many other human diseases.

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ULOGA MEZENHIMALNIH MATIČNIH ĆELIJA U TERAPIJI INFARKTA MIOKARDA

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Mezenhimalne matične ćelije (eng. *Mesenchymal stem cells* (MSCs)) su multipotentne stromalne ćelije koje mogu da se diferenciraju u osteoblaste, hondrocite i adipocite. Početkom 21. veka, *in vivo* studije su pokazale da humane MSCs mogu da transdiferenciraju u ćelije dobijene od endoderma i kardiomiocitni fenotip. Kada kardiomiociti nisu snabdeveni krvlju, kao što je slučaj sa infarktom miokarda, gubitak funkcionalnih kardiomiocita odigrava se putem nekroze, apoptoze i autofagije. Pored prolaska kroz različite faze inflamacije i ozdravljenja, dinamično mikrookruženje u infarciranom tkivu takođe eksprimira citokine, koji promovišu migraciju matičnih ćelija i njihov *homing*. S obzirom na neizvesnu sudbinu miokarda diktiranu stepenom nekroze, postaje jasno da je u cilju boljeg ishoda infarkta miokarda, neophodno pronaći adekvatnu terapiju. Moguće rešenje ove dileme je ciljana terapija matičnim ćelijama.

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Ključne reči: *mezenhimalne matične ćelije, infarkt miokarda, terapija*