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Review Article

Homing of stem cells to ischemic myocardium

Sharven Taghavi[1,3], Jon C George[1,2]

[1]Cardiovascular Research Center; [2]School of Medicine; [3]Hospital Department of Surgery, Temple University, Philadelphia, PA, USA

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Abstract: Progenitor cells have the capability to home myocardium in response to ischemia. Cell adhesion markers, in particular integrins, play an important role in the trafficking of stem cells to myocardium. In addition, damaged myocardium secretes several chemokines and growth factors that recruit these precursor cells to the heart. Nitric oxide synthase and hormones can also contribute to the trafficking of progenitor cells to myocardium. The recruitment of stem cells to ischemic myocardium is a complex interchange between cell adhesion markers, chemokines, and growth factors and a better understanding of these processes may lead to more efficient use of stem cells for therapeutic benefit.

Keywords: Stem cells, ischemic myocardium, myocardial regeneration, growth factors, myocardial infarction

Introduction

The heart was once thought to be a terminally differentiated organ without capacity for regeneration [1, 2]. However, studies have shown that the heart has endogenous cells capable of regeneration [3-5]. In addition, other stem cell types have shown the capacity to repair damaged myocardium [6-8]. This has lead to human trials, which have shown that stem cells can improve cardiac function and regenerate ischemic myocardium [9-11]. After myocardial injury, progenitor cells home to ischemic myocardium where they can attenuate myocardial repair. Mesenchymal stem cells (MSC) and bone marrow derived stem cells (BSCs) have been shown to preferentially home to ischemic myocardium [12-16]. Hematopoietic stem cells (HSCs) [17-20] and cardiac derived stem cells (CSCs) [21, 22] are also recruited to myocardium after ischemic injury. Several cell adhesion markers, chemokines, and growth factors play a role in the recruitment of these progenitor cells to ischemic cardiac tissue.

Cell adhesion markers

Cell adhesion molecules play a key role in recruiting HSCs to myocardium that has undergone ischemic insult. In particular, integrins have been implicated in recruiting stem cells to ischemic tissue. VLA-4 is an integrin involved in the in vivo trafficking of HSCs to sites of injury [23, 24]. BMCs use a different adhesion molecule to traffic to ischemic myocardium. Ip et al showed that blocking of integrin β1 led to a significant reduction in the homing of BMSCs to acutely ischemic myocardium [25]. Another study by the same group demonstrated that integrin β2 (CD18) and its interaction with ICAM-1 plays an essential role in the recruitment of BMSCs to ischemic myocardium [26]. These findings suggest that integrins play a key role in the recruitment of progenitor cells to ischemic myocardium.

Chemokines

Chemotactic factors have also been implicated as HSCs have been shown to migrate to ischemic myocardium in response to stromal-derived factor (SDF)-1-alpha, the ligand for the CXC chemokine receptor 4 (CXCR4) [17-20]. Further studies showed that SDF-1 increases the homing of stem cells to myocardium when ischemic injury is present [27]. In addition, SDF-1 has been shown to induce transcoronary migration of stem cells into infarcted myocardium [28]. The use of a tissue-engineered extracellular matrix scaffold seeded with endothelial

Table 1. A Summary of Growth Factors Involved in the Homing of Stem Cells to Ischemic Myocardium

Growth Factor	Cells Affected	Characteristic
Stem Cell Factor (SCF)	c-Kit+ cells	Increases stem cells into the circulation and translocation into ischemic myocardium.
Vascular Endothelial Growth Factor (VEGF)	CD34+ cells	Upregulated by ischemic myocardium and attracts stem cells to the area of injury
Neural Growth Factor (NGF)	CD34+ and c-Kit+ cells	Results in increased angiogenesis and increases the amount of SCF in the circulation.
Granulocyte-Colony Stimulating Factor (G-CSF)	White blood cells, CD34+	Increases progenitor cells and white blood cells into the peripheral circulation.
Insulin-Like Growth Factor (IGF)	Cardiac derived stem cells	Works in paracrine fashion to attract endogenous cardiac stem cells to the infarct border zone.
Hepatocyte Growth Factor (HGF)	Bone marrow and cardiac derived stem cells	Mobilize stem cells from bone marrow to myocardium, attracts endogenous cardiac stem cells to areas of infarction.
Fibroblast growth factor (FGF)	Unknown	Unknown

progenitor cells primed with SDF induced neovasculogenesis in the myocardial infarct borderzone and preserved ventricular function after infarct [29]. In addition, because SDF is rapidly cleaved by proteases in injured tissue, a protease resistant SDF was designed and used to treat animals with acute myocardial infarction. The protease resistant version of SDF promoted greater recruitment of stem cells and had greater improvement of cardiac function after MI [30]. Treatment with mesenchymal stem cells alone has been shown to upregulate the expression of SDF by ischemic heart tissue, leading to the recruitment of more stem cells [31].

Monocyte chemotactic protein-1 (MCP-1) is another chemokine involved in the homing of stem cells to ischemic myocardium. Neural crest stem cells were found to migrate and accumulate at the ischemic border zone area of infarcted hearts in response to MCP-1 and the use of an MCP-1 antibody significantly depressed this chemotactic effect [32]. Monocyte chemotactic protein-3 (MCP-3) is a chemokine that induces mesenchymal stem cell homing to ischemic myocardium. MCP-3 is transiently expressed in myocardial tissue after acute myocardial infarction and results in the trafficking of MSCs to the infarcted myocardium. The authors did not find regeneration of cardiac myocytes by these MSCs but did note beneficial remodeling in the infarct zone [33].

Interleukins have also been shown to recruit HSCs to the periphery [34, 35] although the role of interleukins in the homing of stem cells to ischemic myocardium needs further investigation.

Growth factors

A summary of growth factors involved in the homing of stem cells to ischemic myocardium is shown in **Table 1**. Stem cell factor (SCF) is a potent recruitor of BMCs, especially for cells that are c-Kit+ (CD117) as SCF is the ligand for c-Kit. Treatment with SCF can increase the number of c-Kit+ cells in the circulation up to 250-fold [36]. Treatment with SCF in acute MI leads to mobilization of c-Kit+ cells and translocation of these cells to the area of infarct. These cells can then go on to induce myocardial regeneration and repair [37]. In another study, mesenchymal stem cells and SCF-overproducing mesenchymal stem cells were compared as treatment modalities in acute myocardial infarction. Stem cell factor overproduction resulted in greater functional benefit due to a paracrine effect on endogenous stem cells in the injured heart [38]. Another study induced acute myocardial infarction in mice with cardiomyocyte-specific overexpression of the membrane-associated isoform of human SCF. These mice had greater endothelial progenitor cell (EPC) recruitment and capillary density after myocardial infarction. These mice also had less cardiac hypertrophy and improved cardiac function after myocardial infarction [39].

Vascular endothelial growth factor (VEGF) is another growth factor involved in the recruitment of stem cells to ischemic myocardium.

Animal studies have shown that stem cells home to ischemic myocardium in response to VEGF [40]. Like SDF, it is upregulated by ischemic myocardium in the presence of mesenchymal stem cells [31]. In humans, VEGF levels peak 7 days after acute MI, correlating with the numbers of circulating CD34+ mononuclear cells [41].

Neural growth factor (NGF) also appears to recruit stem cells to ischemic myocardium. It is expressed in infarcted human myocardium [42]. Treatment of mice undergoing myocardial infarction with antibodies specific to NGF resulted in decreased angiogenesis and worsened cardiac function. However, when mice overexpressing NGF underwent myocardial infarction, there was increased neovascularization and cardiac function. In addition, mice over expressing NGF had increased stem cell factor and higher abundance of c-kit+ stem cells in the infarcted heart, suggesting that one of the mechanisms in which NGF improves cardiac function is through the recruitment of c-Kit+ stem cells [42].

Several studies have shown that granulocyte-colony stimulating factor (G-CSF) plays a key role in the recruitment and mobilization of progenitor cells to ischemic myocardium [37, 43-47]. When administered systemically, G-CSF appears to recruit stem cells from bone marrow [43, 44]. Human trials have also studied the use of G-CSF in patients suffering from myocardial infarction [48, 49]. Zohlnhofer et al. showed that systemic treatment of patients undergoing percutaneous coronary intervention with G-CSF led to an increase in circulating white blood cells and CD34+ but did not result in improved cardiac function for these patients [49].

Insulin-like growth factor (IGF) plays a key role in the homing of stem cells to ischemic myocardium. Anversa et al. showed that IGF expression is upregulated after acute myocardial infarction [21] and that CSCs express IGF receptors [50]. The injection growth factors such as IGF into ischemic myocardium leads to greater repair of infarcted myocardium by resident cardiac progenitor cells and injected cardiac derived stem cells [51]. A gradient of IGF established at the border zone of a myocardial infarct resulted in the recruitment of endogenous CSCs. These CSCs went on to induce myocardial regeneration and led to improved survival and decreased infarcts [50]. Another study used IGF tethered to peptide nanofibers and determined that co-treatment of these IGF nanofibers with CSC treatment resulted in greater improvement of myocardial structure and function than treatment with CSCs alone [52].

Hepatocyte Growth Factor (HGF) plays a role in the recruitment of stem cells to ischemic myocardium. HGF expression is regulated in cardiac tissue after myocardial infarction [18]. Bone marrow derived stem cells are attracted to the upregulated HGF and leave the peripheral circulation to home to the infarcted myocardium [18]. HGF is also a powerful chemoattractant for cardiac progenitor cells that reside in the adult heart. Treatment of myocardial infarcts with HGF leads to increased homing of these resident cardiac progenitor cells to the infarcted myocardium and regeneration of myocardium [51]. This regenerated myocardium contains arterioles and capillaries and functional myocytes [50].

Fibroblast growth factor (FGF) also appears to play a role in recruitment of stem cells to ischemic myocardium, however, it has not been studied as extensively as other growth factors. Serum levels of FGF in humans appear to increase in response to acute myocardial infarction [53]. In addition, treatment of acute MI with mesenchymal stem cells in an animal model has shown to result in increased expression of FGF by cardiac tissue, suggesting that it plays a role in the homing of these stem cells cells to the infarct zone [31]. The role of FGF in the recruitment of stem cells to ischemic myocardium needs greater investigation and its potential as a therapeutic chemokine merits further studies.

Endothelial nitric oxide synthase

Endothelial nitric oxide synthase (eNOS) is an essential component for neovascularization. Nitric oxide synthase knock-out mice have impaired neovascularization and decreased mobilization of EPCs, indicating that eNOS expressed by BSCs influence the recruitment of stem cells. These mice also showed reduced expression of VEGF and matrix metalloproteinase-9 (MMP-9), which may explain the mechanism of eNOS induced stem cell mobilization

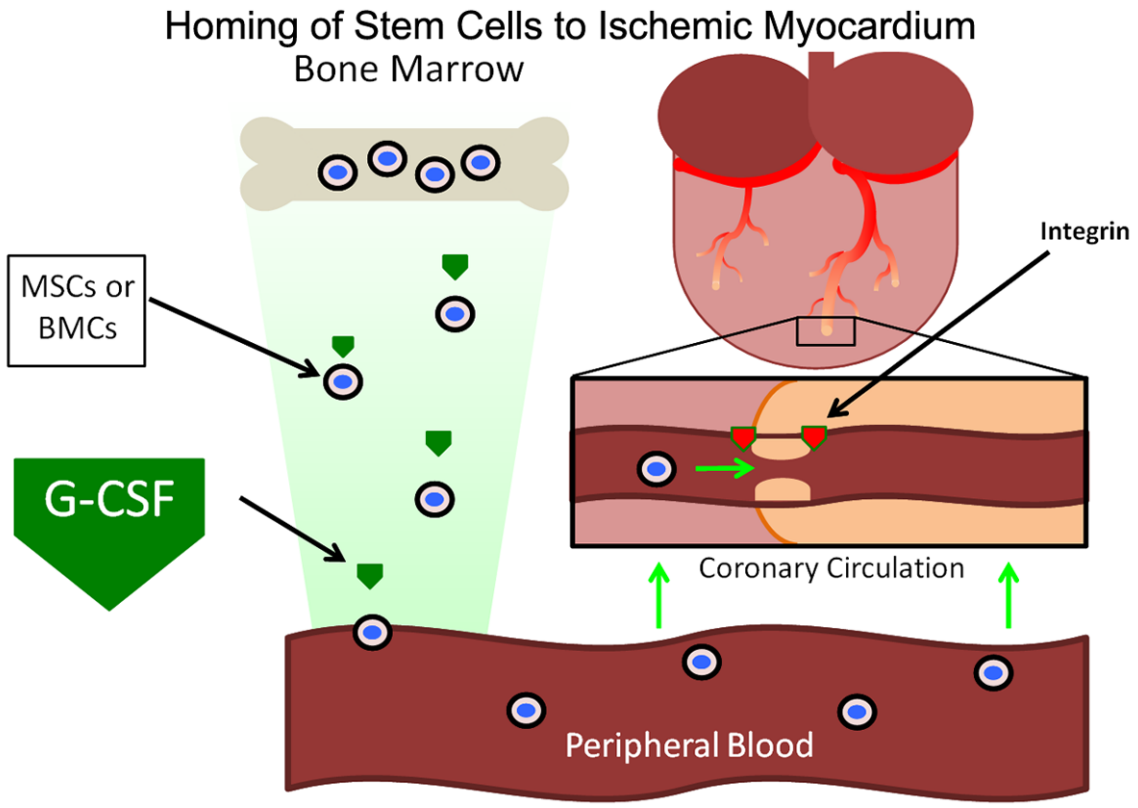

Figure 1. Mesenchymal stem cells (MSCs), bone marrow derived stem cells (BMCs), and hematopoietic derived stem cells are recruited to ischemic myocardium through a complex interplay between growth factors (G-CSF) and cell adhesion markers (integrin).

[54, 55]. The role of eNOS in the mobilization of BMSCs has been established in both hind-leg ischemia [54, 55] models and myocardial infarction models [56].

Hormones

Erythropoietin has also been shown to improve cardiac function by inducing neovascularization. This neovascularization is related to increased mobilization and incorporation of bone marrow derived endothelial progenitor cells [40]. In addition, the erythropoietin treated group had a 4.5 fold increase in VEGF expressed by ischemic myocardium [40]. Erythropoietin has been shown to lead to preferential homing of endothelial progenitor cells to the ischemic border zone of myocardial infarcts resulting in improved microvascularization of ischemic cardiac tissue [57].

Estrogen appears to play a role in the mobilization of endothelial progenitor cells to ischemic myocardium. Hamada et al. showed that estrogen knock-out mice had impaired homing of endothelial progenitors cells to ischemic myocardium. These knock out mice also had decreased mobilization of EPCs from bone marrow to peripheral circulation. This study also showed that estrogen appeared to upregulate the expression of VEGF-A by EPCs. This increase in VEGF-A may explain the mechanism of estrogen's effect on EPC biology [58]. Another study reinforced the ability of estrogen to increase the number of circulating EPCs after ischemic myocardial injury. This study showed that estrogen augmented the mobilization and incorporation of bone marrow derived EPCs into sites of neovascularization by endothelial nitric oxide synthase-mediated activation of matrix metalloproteinase-9 [59]. The role of nitric oxide synthase in the recruitment of progenitor cells to ischemic myocardium is supported in previously mentioned studies [54-56].

Conclusions

Knowledge of stem cell recruitment to ischemic myocardium has led to human trials testing the ability of stem cell therapy to improve cardiac

function [60-65]. The mechanism by which stem cells home to ischemic myocardium is a complex interplay of cell adhesion markers, chemokines, growth factors, and even hormones. A schematic of this interplay is shown **Figure 1**. These mechanisms of stem cell homing can be used therapeutically to maximize the numbers of progenitor cells that are recruited to and engraft into ischemic myocardium. Further studies are needed to determine how to best use these homing mechanisms for therapeutics.

Address correspondence to: Dr. Jon C George, Cardiovascular Research Center; School of Medicine, Temple University, Philadelphia, PA, USA. E-mail: jcgeorgemd@hotmail.com

References

[1] Zak R. Development and proliferative capacity of cardiac muscle cells. Circ Res 1974; 34: 17-26.

[2] Soonpaa MH and Field LJ. Survey of studies examining mammalian cardiomyocyte DNA synthesis. Circ Res 1998; 83: 15-26.

[3] Angert D, Berretta RM, Kubo H, Zhang H, Chen X, Wang W, Ogorek B, Barbe M and Houser SR. Repair of the injured adult heart involves new myocytes potentially derived from resident cardiac stem cells. Circ Res 2011; 108: 1226-1237.

[4] Anversa P and Kajstura J. Ventricular myocytes are not terminally differentiated in the adult mammalian heart. Circ Research 1998; 83: 1-14.

[5] Beltrami AP, Barlucchi L, Torella D, Baker M, Limana F, Chimenti S, Kasahara H, Rota M, Musso E and Urbanek K. Adult cardiac stem cells are multipotent and support myocardial regeneration. Cell 2003; 114: 763-776.

[6] Kajstura J, Rota M, Whang B, Cascapera S, Hosoda T, Bearzi C, Nurzynska D, Kasahara H, Zias E, Bonafe M, Nadal-Ginard B, Torella D, Nascimbene A, Quaini F, Urbanek K, Leri A, Anversa P. Bone marrow cells differentiate in cardiac cell lineages after infarction independently of cell fusion. Circ Res 2005; 96: 127-137.

[7] Kinnaird T, Stabile E, Burnett M, Lee C, Barr S, Fuchs S and Epstein S. Marrow-derived stromal cells express genes encoding a broad spectrum of arteriogenic cytokines and promote in vitro and in vivo arteriogenesis through paracrine mechanisms. Circ Res 2004; 94: 678-685.

[8] Kinnaird T, Stabile E, Burnett M, Shou M, Lee C, Barr S, Fuchs S, Epstein S. Local delivery of marrow-derived stromal cells augments collateral perfusion through paracrine mechanisms. Circulation 2004; 109: 1543-1549.

[9] Anversa P, Nadal-Ginard B. Myocyte renewal and ventricular remodelling. Nature 2002; 415: 240-243.

[10] Bolli R, Chugh AR, D'Amario D, Loughran JH, Stoddard MF, Ikram S, Beache GM, Wagner SG, Leri A, Hosoda T. Cardiac stem cells in patients with ischaemic cardiomyopathy (SCIPIO): initial results of a randomised phase 1 trial. Lancet 2011; 378: 1847-1857.

[11] Schachinger V, Erbs S, Elsasser A, Haberbosch W, Hambrecht R, Holschermann H, Yu J, Corti R, Mathey DG, Hamm CW, Suselbeck T, Werner N, Haase J, Nuezner J, Gernming A, Mark B, Assmus B, Tonn T, Dimmeler S, Zeiher AM. Improved clinical outcome after intracoronary administration of bone-marrow-derived progenitor cells in acute myocardial infarction: final 1-year results of the REPAIR-AMI trial. Eur Heart J 2006; 27: 2775-2783.

[12] Mouquet F, Pfister O, Jain M, Oikonomopoulos A, Ngoy S, Summer R, Fine A, Liao R. Restoration of cardiac progenitor cells after myocardial infarction by self-proliferation and selective homing of bone marrow-derived stem cells. Circ Res 2005; 97: 1090-1092.

[13] Nagaya N, Fujii T, Iwase T, Ohgushi H, Itoh T, Uematsu M, Yamagishi M, Mori H, Kangawa K, Kitamura S. Intravenous administration of mesenchymal stem cells improves cardiac function in rats with acute myocardial infarction through angiogenesis and myogenesis. Am J Physiol Heart Circ Physiol 2004; 287: 2670-2676.

[14] Martin B, Meyers J, Kuang J, Smith A. Allogeneic mesenchymal stem cell engraftment in the infarcted rat myocardium: timing and delivery route. Bone Marrow Transplant 2002; 29: 144.

[15] Pittenger MF, Martin BJ. Mesenchymal Stem Cells and Their Potential as Cardiac Therapeutics. Circ Res 2004; 95: 9-20.

[16] Sheikh AY, Lin SA, Cao F, Cao Y, van der Bogt KEA, Chu P, Chang CP, Contag CH, Robbins RC, Wu JC. Molecular Imaging of Bone Marrow Mononuclear Cell Homing and Engraftment in Ischemic Myocardium. Stem Cells 2007; 25: 2677-2684.

[17] Askari AT, Unzek S, Popovic ZB, Goldman CK, Forudi F, Kiedrowski M, Rovner A, Ellis SG, Thomas JD, DiCorleto PE, Topol EJ and Penn MS. Effect of stromal-cell-derived factor 1 on stem-cell homing and tissue regeneration in ischaemic cardiomyopathy. Lancet 2003; 362: 697-703.

[18] Kucia M, Dawn B, Hunt G, Guo Y, Wysoczynski M, Majka M, Ratajczak J, Rezzoug F, Ildstad ST, Bolli R, Ratajczak MZ. Cells expressing early

cardiac markers reside in the bone marrow and are mobilized into the peripheral blood after myocardial infarction. Circ Res 2004; 95: 1191-1199.

[19] Ma J, Ge J, Zhang S, Sun A, Shen J, Chen L, Wang K, Zou Y. Time course of myocardial stromal cell–derived factor 1 expression and beneficial effects of intravenously administered bone marrow stem cells in rats with experimental myocardial infarction. Basic Res Cardiol 2005; 100: 217-223.

[20] Wright DE, Bowman EP, Wagers AJ, Butcher EC, Weissman IL. Hematopoietic Stem Cells Are Uniquely Selective in Their Migratory Response to Chemokines. J Exp Med 2002; 195: 1145-1154.

[21] Anversa P, Reiss K, Kajstura J, Cheng W, Li P, Sonnenblick E, Olivetti G. Myocardial infarction and the myocyte IGF1 autocrine system. Eur Heart J 1995; 16: 37.

[22] Urbanek K, Rota M, Cascapera S, Bearzi C, Nascimbene A, De Angelis A, Hosoda T, Chimenti S, Baker M, Limana F, Nurzynska D, Torella D, Rotatori F, Rastaldo R, Musso E, Quaini F, Leri A, Kajstura J, Anversa P. Cardiac Stem Cells Possess Growth Factor-Receptor Systems That After Activation Regenerate the Infarcted Myocardium, Improving Ventricular Function and Long-Term Survival. Circ Res 2005; 97: 663-673.

[23] Papayannopoulou T, Craddock C, Nakamoto B, Priestley GV, Wolf NS. The VLA4/VCAM-1 adhesion pathway defines contrasting mechanisms of lodgement of transplanted murine hemopoietic progenitors between bone marrow and spleen. Proc Natl Acad Sci 1995; 92: 9647-9651.

[24] Papayannopoulou T and Nakamoto B. Peripheralization of hemopoietic progenitors in primates treated with anti-VLA4 integrin. Proc Natl Acad Sci 1993; 90: 9374-9378.

[25] Ip JE, Wu Y, Huang J, Zhang L, Pratt RE, Dzau VJ. Mesenchymal Stem Cells Use Integrin B1 Not CXC Chemokine Receptor 4 for Myocardial Migration and Engraftment. Mol Biol Cell 2007; 18: 2873-2882.

[26] Wu Y, Ip JE, Huang J, Zhang L, Matsushita K, Liew CC, Pratt RE, Dzau VJ. Essential role of ICAM-1/CD18 in mediating EPC recruitment, angiogenesis, and repair to the infarcted myocardium. Circ Res 2006; 99: 315-322.

[27] Abbott JD, Huang Y, Liu D, Hickey R, Krause DS, Giordano FJ. Stromal Cell-Derived Factor-1a plays a critical role in stem cell recruitment to the heart after myocardial infarction but is not sufficient to induce homing in the absence of injury. Circulation 2004; 110: 3300-3305.

[28] Dawn B, Stein AB, Urbanek K, Rota M, Whang B, Rastaldo R, Torella D, Tang XL, Rezazadeh A, Kajstura J, Leri A, Hunt G, Varma J, Prabhu SD, Anversa P, Bolli R. Cardiac stem cells delivered intravascularly traverse the vessel barrier, regenerate infarcted myocardium, and improve cardiac function. Proc Natl Acad Sci 2005; 102: 3766-3771.

[29] Frederick JR, Fitzpatrick JR 3rd, McCormick RC, Harris DA, Kim AY, Muenzer JR, Marotta N, Smith MJ, Cohen JE, Hiesinger W, Atluri P, Woo YJ. Stromal cell-derived factor-1alpha activation of tissue-engineered endothelial progenitor cell matrix enhances ventricular function after myocardial infarction by inducing neovasculogenesis. Circulation 2010; 122: 107-117.

[30] Segers VFM, Tokunou T, Higgins LJ, MacGillivray C, Gannon J, Lee RT. Local delivery of protease-resistant stromal cell derived factor-1 for stem cell recruitment after myocardial infarction. Circulation 2007; 116: 1683-1692.

[31] Tang YL, Zhao Q, Qin X, Shen L, Cheng L, Ge J, Phillips MI. Paracrine action enhances the effects of autologous mesenchymal stem cell transplantation on vascular regeneration in rat model of myocardial infarction. Ann Thorac Surg 2005; 80: 229-237.

[32] Tamura Y, Matsumura K, Sano M, Tabata H, Kimura K, Ieda M, Arai T, Ohno Y, Kanazawa H, Yuasa S, Kaneda R, Makino S, Nakajima K, Okano H, Fukuda K. Neural crest-derived stem cells migrate and differentiate into cardiomyocytes after myocardial infarction. Arterioscler Thromb Vasc Biol 2011; 31: 582-589.

[33] Schenk S, Mal N, Finan A, Zhang M, Kiedrowski M, Popovic Z, McCarthy PM, Penn MS. Monocyte Chemotactic protein-3 ss a myocardial mesenchymal stem cell homing factor. Stem Cells 2007; 25: 245-251.

[34] Laterveer L, Lindley I, Hamilton M, Willemze R, Fibbe W. Interleukin-8 induces rapid mobilization of hematopoietic stem cells with radioprotective capacity and long-term myelolymphoid repopulating ability. Blood 1995; 85: 2269-2275.

[35] Laterveer L, Lindley I, Heemskerk D, Camps J, Pauwels E, Willemze R, Fibbe W. Rapid mobilization of hematopoietic progenitor cells in rhesus monkeys by a single intravenous injection of interleukin-8. Blood 1996; 87: 781-788.

[36] Bodine D, Seidel N, Gale M, Nienhuis A, Orlic D. Efficient retrovirus transduction of mouse pluripotent hematopoietic stem cells mobilized into the peripheral blood by treatment with granulocyte colony-stimulating factor and stem cell factor. Blood 1994; 84: 1482-1491.

[37] Orlic D, Kajstura J, Chimenti S, Limana F, Jakoniuk I, Quaini F, Nadal-Ginard B, Bodine DM, Leri A, Anversa P. Mobilized bone marrow cells repair the infarcted heart, improving function

and survival. Proc Natl Acad Sci 2001; 98: 10344.

[38] Fazel S, Chen L, Weisel RD, Angoulvant D, Seneviratne C, Fazel A, Cheung P, Lam J, Fedak PWM, Yau TM. Cell transplantation preserves cardiac function after infarction by infarct stabilization: augmentation by stem cell factor. J Thorac Cardiovasc Surg 2005; 130: 1310.

[39] Xiang FL, Lu X, Hammoud L, Zhu P, Chidiac P, Robbins J, Feng Q. Cardiomyocyte-specific overexpression of human stem cell factor improves cardiac function and survival after myocardial infarction in mice. Circulation 2009; 120: 1065-1074.

[40] Westenbrink BD, Lipsic E, van der Meer P, van der Harst P, Oeseburg H, Du Marchie Sarvaas GJ, Koster J, Voors AA, van Veldhuisen DJ, van Gilst WH, Schoemaker RG. Erythropoietin improves cardiac function through endothelial progenitor cell and vascular endothelial growth factor mediated neovascularization. Eur Heart J 2007; 28: 2018-2027.

[41] Shintani S, Murohara T, Ikeda H, Ueno T, Honma T, Katoh A, Sasaki K, Shimada T, Oike Y, Imaizumi T. Mobilization of endothelial progenitor cells in patients with acute myocardial infarction. Circulation 2001; 103: 2776-2779.

[42] Meloni M, Caporali A, Graiani G, Lagrasta C, Katare R, Van Linthout S, Spillmann F, Campesi I, Madeddu P, Quaini F, Emanueli C. Nerve growth factor promotes cardiac repair following myocardial infarction. Circulation Research 2010; 106: 1275-1284.

[43] Fukuhara S, Tomita S, Nakatani T, Ohtsu Y, Ishida M, Yutani C, Kitamura S. G-CSF promotes bone marrow cells to migrate into infarcted mice heart, and differentiate into cardiomyocytes. Cell Transplant 2004; 7: 741-748.

[44] Kawada H, Fujita J, Kinjo K, Matsuzaki Y, Tsuma M, Miyatake H, Muguruma Y, Tsuboi K, Itabashi Y, Ikeda Y, Ogawa S, Okano H, Hotta T, Ando K, Fukuda K. Nonhematopoietic mesenchymal stem cells can be mobilized and differentiate into cardiomyocytes after myocardial infarction. Blood 2004; 104: 3581-3587.

[45] Kocher A, Schuster M, Szabolcs M, Takuma S, Burkhoff D, Wang J, Homma S, Edwards N, Itescu S. Neovascularization of ischemic myocardium by human bone-marrow-derived angioblasts prevents cardiomyocyte apoptosis, reduces remodeling and improves cardiac function. Nat Med 2001; 7: 430-436.

[46] Lapidot T, Petit I. Current understanding of stem cell mobilization: The roles of chemokines, proteolytic enzymes, adhesion molecules, cytokines, and stromal cells. Exp Hem 2002; 30: 973-981.

[47] Ohtsuka M, Takano H, Zou Y, Toko H, Akazawa H, Qin Y, Suzuki M, Hasegawa H, Nakaya H, Komuro I. Cytokine therapy prevents left ventricular remodeling and dysfunction after myocardial infarction through neovascularization. FASEB K 2004; 18: 851-853.

[48] Kang HJ, Lee HY, Na SH, Chang SA, Park KW, Kim HK, Kim SY, Chang HJ, Lee W, Kang WJ, Koo BK, Kim YJ, Lee DS, Sohn DW, Han KS, Oh BH, Park YB, Kim HS. Differential effect of intracoronary infusion of mobilized peripheral blood stem cells by granulocyte colony-stimulating factor on left ventricular function and remodeling in patients with acute myocardial infarction versus old myocardial infarction: The MAGIC cell-3-DES randomized, controlled trial. Circulation 2006; 114: 145-151.

[49] Zohlnhofer D, Ott I, Mehilli J, Schomig K, Michalk F, Ibrahim T, Meisetschlager G, von Wedel J, Bollwein H, Seyfarth M, Dirschinger J, Schmitt C, Schwaiger M, Kastrati A, Schomig A. Stem cell mobilization by granulocyte colony-stimulating factor in patients with acute myocardial infarction. JAMA 2006; 295: 1003-1010.

[50] Urbanek K, Rota M, Cascapera S, Bearzi C, Nascimbene A, De Angelis A, Hosoda T, Chimenti S, Baker M, Limana F. Cardiac stem cells possess growth factor-receptor systems that after activation regenerate the infarcted myocardium, improving ventricular function and long-term survival. Circ Res 2005; 97: 663-673.

[51] Rota M, Padin-Iruegas ME, Misao Y, De Angelis A, Maestroni S, Ferreira-Martins J, Fiumana E, Rastaldo R, Arcarese ML, Mitchell TS, Boni A, Bolli R, Urbanek K, Hosoda T, Anversa P, Leri A Kajstura J. Local activation or implantation of cardiac progenitor cells rescues scarred infarcted myocardium improving cardiac function. Circ Res 2008; 103: 107-116.

[52] Padin-Iruegas ME, Misao Y, Davis ME, Segers VFM, Esposito G, Tokunou T, Urbanek K, Hosoda T, Rota M, Anversa P. Cardiac progenitor cells and biotinylated insulin-like growth factor-1 nanofibers improve endogenous and exogenous myocardial regeneration after infarction. Circulation 2009; 120: 876-887.

[53] Wang Y, Johnsen HE, Mortensen S, Bindslev L, Sejersten Ripa R, Haack-Sorensen M, Jorgensen E, Fang W, Kastrup J. Changes in circulating mesenchymal stem cells, stem cell homing factor, and vascular growth factors in patients with acute ST elevation myocardial infarction treated with primary percutaneous coronary intervention. Heart 2006; 92: 768-774.

[54] Aicher A, Heeschen C, Mildner-Rihm C, Urbich C, Ihling C, Technau-Ihling K, Zeiher AM, Dimmeler S. Essential role of endothelial nitric ox-

ide synthase for mobilization of stem and progenitor cells. Net Med 2003; 9: 1370-1376.

[55] Yu J, DeMuinck ED, Zhuang Z, Drinane M, Kauser K, Rubanyi GM, Qian HS, Murata T, Escalante B, Sessa WC. Endothelial nitric oxide synthase is critical for ischemic remodeling, mural cell recruitment, and blood flow reserve. Proc Natl Acad Sci 2005; 102: 10999-11004.

[56] Ii M, Nishimura H, Iwakura A, Wecker A, Eaton E, Asahara T, Losordo DW. Endothelial progenitor cells are rapidly recruited to myocardium and mediate protective effect of ischemic preconditioning via "imported" nitric oxide synthase activity. Circulation 2005; 111: 1114-1120.

[57] Westenbrink BD, Oeseburg H, Kleijn L, van der Harst P, Belonje AMS, Voors AA, Schoemaker RG, de Boer RA, van Veldhuisen DJ, van Gilst WH. Erythropoietin stimulates normal endothelial progenitor cell-mediated endothelial turnover, but attributes to neovascularization only in the presence of local ischemia. Eur Heart J 2007; 22: 265-274.

[58] Hamada H, Kim MK, Iwakura A, Ii M, Thorne T, Qin G, Asai J, Tsutsumi Y, Sekiguchi H, Silver M, Wecker A, Bord E, Zhu Y, Kishore R, Losordo DW. Estrogen receptors alpha and beta mediate contribution of bone marrow-derived endothelial progenitor cells to functional recovery after myocardial infarction. Circulation 2006; 114: 2261-2270.

[59] Iwakura A, Shastry S, Luedemann C, Hamada H, Kawamoto A, Kishore R, Zhu Y, Qin G, Silver M, Thorne T, Eaton L, Masuda H, Asahara T, Losordo DW. Estradiol enhances recovery after myocardial infarction by augmenting incorporation of bone marrow-derived endothelial progenitor cells into sites of ischemia-induced neovascularization via endothelial nitric oxide synthase-mediated activation of matrix metalloproteinase-9. Circulation 2006; 113: 1605-1614.

[60] Blocklet D, Toungouz M, Berkenboom G, Lambermont M, Unger P, Preumont N, Stoupel E, Egrise D, Degaute JP, Goldman M. Myocardial homing of nonmobilized peripheral blood CD34+ cells after intracoronary injection. Stem Cells 2006; 24: 333-336.

[61] Dedobbeleer C, Blocklet D, Toungouz M, Lambermont M, Unger P, Degaute JP, Goldman S, Berkenboom G. Myocardial homing and coronary endothelial function after autologous blood CD34+ progenitor cells intracoronary injection in the chronic phase of myocardial infarction. J Cardiovasc Pharmacol 2009; 53: 480-485.

[62] Hofmann M, Wollert KC, Meyer GP, Menke A, Arseniev L, Hertenstein B, Ganser A, Knapp WH, Drexler H. Monitoring of bone marrow cell homing into the infarcted human myocardium. Circulation 2005; 111: 2198-2202.

[63] Schachinger V, Aicher A, Dobert N, Rover R, Diener J, Fichtlscherer S, Assmus B, Seeger FH, Menzel C, Brenner W, Dimmeler S, Zeiher AM. Pilot trial on determinants of progenitor cell recruitment to the infarcted human myocardium. Circulation 2008; 118: 1425-1432.

[64] Shintani S, Murohara T, Ikeda H, Ueno T, Honma T, Katoh A, Sasaki K, Shimada T, Oike Y, Imaizumi T. Mobilization of endothelial progenitor cells in patients with acute myocardial infarction. Circulation 2001; 103: 2776-2779.

[65] Spevack DM, Cavaleri S, Zolotarev A, Liebes L, Inghirami G, Tunick PA and Kronzon I. Increase in circulating bone marrow progenitor cells after myocardial infarction. Coron Artery Dis 2006; 17: 345-349.