J. Cell. Mol. Med. Vol 16, No 6, 2012 pp. 1203-1205

A novel method to delivery stem cells to the injured heart: spatially focused magnetic targeting strategy

Zheyong Huang [a, #], Ning Pei [b, #], Yunli Shen [a, #], Yongyong Gong [b], Xinxing Xie [a], Xiaoning Sun [a], Yunzeng Zou [a], Juying Qian [a], Aijun Sun [a, *], Junbo Ge [a, *]

[a] *Shanghai Institute of Cardiovascular Diseases, Zhongshan Hospital, Fudan University, Shanghai, China*
[b] *College of Science, Shanghai University, Shanghai, China*

Received: March 19, 2012; Accepted: April 6, 2012

Introduction and background

Given the adult heart's minimal capacity for endogenous regeneration, cell therapy has emerged as a promising approach to the regeneration of damaged vascular and cardiac tissue after acute myocardial infarction and heart failure. However, systematic review suggests only mild improvement in global heart function, and high degree of heterogeneity among clinical trials [1]. The first prerequisite for cell therapy success is the engraftment and thus, homing of transplanted cells to the target area. Poor cell homing, retention and engraftment are major obstacles in achieving a significant functional benefit irrespective of the cell type or delivery route used. Data showed only 1–3% of the delivered cells were recruited at the infarct sites *via* intracoronary administration. The retention of cells in the heart is extremely low, even undetectable after a few weeks when administered by the intravenous route [2–5]. The predominant number of cells was found in non-targeting organs such as liver, spleen and lung.

To induce migration and homing of transplanted cells to optimize the efficacy of cell-based therapies, much efforts have been made in identifying chemokine and its receptors (CXCR4/SDF-1 axis, *et al.*) in the last decades [6, 7]. However, due to the extreme complicity of the 'cell-extracellular matrix-cytokine' network and the homing molecular mechanisms, the chemoattractant molecules-targeted method has been far away from being able to precisely and effectively regulate stem cell migrating to target tissue [8, 9].

Magnetic targeting strategy, traditionally used in chemotherapy for tumour [10], had been introduced to localize magnetic nanoparticle-loaded cell delivery to target lesion *in vivo* in recent years [11–17]. The accumulation and retention of the magnetic responsive cells can be enhanced by using an external magnetic field produced by electromagnet, which is focused on the area of interest [18]. Cheng K *et al.* [19] were the first to introduce magnetic targeting strategy to attract transplanted cells to the heart. Using a 1.3 Tesla magnet applied above the rat apex during the intramyocardial injection of magnetic responsive cardiosphere-derived cells, they found that cell retention and engraftment in the recipient hearts increased by approximately threefold compared to non-targeted cells. Chaudeurge A *et al.* [20] adopted subcutaneous insertion of a magnet over the chest cavity during therapeutic intracavitary stem cell infusion, found that the average number of engrafted cells was significantly 10 times higher with than without magnetic targeting. This magnetically enhanced intracoronary cell delivery was confirmed by another study [21]. Thus, magnetic targeting is proved to enhance cell retention, engraftment and this novel method to improve cell therapy outcome offers the potential for clinical applications.

However, the magnetic field has some inherent limitations as the magnetic flux density is maximal at the magnet pole face and cannot be focused at a distance from the magnet [10]. For conventional electromagnet therefore magnetically loaded cells are predominantly attracted to the surface of magnetic materials, and hard to be targeted to tissues localized deeper in the body. To promote the cell retention at targeting sites remote from the magnet surface, a greater magnetic force or invasive approaches (e.g. implant magnetized stent, magnetic particles or magnet at the target site) will be required. Magnetically loaded endothelial cells were homing to the magnetized stent deployed in rat arteries in the presence of a uniform magnetic field [12, 13]. However, achievement of the cell engraftment necessary for therapeutic effects by using a 'safe magnet force' would be challenging. Moreover, it is not feasible that there could be the invasive implantation of a magnet or magnetized materials in parenchymatous organs such as heart.

To overcome these limitations, it is of great significance to develope a magnetic field which can be focused at a distance from the

[#]Three authors contributed equally to this work.
*Correspondence to: Junbo GE, MD, FACC., FESC., FSCAI., or Aijun SUN, MD, Shanghai Institute of Cardiovascular Diseases, Zhongshan Hospital, Fudan University, 180 Feng Lin Road, Shanghai 200032, China.
Tel.: +86 21 64041990x2153
Fax: +86 21 64223006
E-mail: junboge@126.com

doi: 10.1111/j.1582-4934.2012.01581.x

magnet surface. Recently, we proposed that the spatially focused magnetic field is feasible in theoretical considerations [22]. Its deep capture property of this special magnetic field has been testified in our preliminary *in vitro* study [22, 23]. The deep accumulation of magnetically loaded mesenchymal stem cells was observed while cells flowed through a tube served as a model of blood vessels in such a magnetic field. The cell capture efficiency was positively influenced by the magnetic flux density, and negatively influenced by the flow velocity. The capture efficiency reached 89.3% with 640 mT of the magnetic flux density, 38.4 T/m of the magnetic intensity gradient and 0.8 mm/sec. of flow velocity in our *in vitro* study [23].

Hypothesis

Based on available studies, it is logical to assume that spatially focused magnetic targeting strategy should be a novel method to deliver stem cells to the injured heart. The hypothesis could be verified in animal study. First, stem cells (such as bone marrow mesenchymal stem cells, *et al.*) are preloaded with biodegradable superparamagnetic iron oxide nanoparticles (SPIO) and became magnetically responsive. Secondly, the magnetically loaded cells are administered intravenously into rats with myocardial infarction, meanwhile a spatially focusing magnetic field is adopted at the area of injured heart. As a result, systemically delivered stem cells will be localized to infarcted heart. The mechanism of this phenomenon should be studied based on electrodynamic and magnetomechanic principles.

Implication

This magnetic spatial localization strategy may revive the route of peripheral intravenous administration for cell therapy. Peripheral systemic intravenous administration is the most convenient rout of cell delivery, offering the advantages of a non-surgical and non-interventional method that can be performed repeatedly. However, it's efficacy was not efficient because the majority of intravenously injected cells were entrapped in lung, and chemoattractant factors secreted by the infarcted heart might be too diluted to attract stem cells [24]. The spatial localization strategy can also performed non-invasively and repeatedly, without the need of a magnet applied on the surface of the heart. So more benefits may be reasonably expected from the combination of the novel magnetic strategy and the systemic intravenous transplantation method, which offers a brand-new, attracting method to effectively overcome the shortcoming of low homing, and subsequently improve the efficacy of cell transplantation for myocardial infarction and heart failure.

More importantly, the magnetic spatial localization strategy may be a breakthrough in targeting therapy, with the potential for widening the indication of magnetic cells/drugs targeting for lesions localized deeper in the body. Its indications are more than just cell therapy in heart. It can be applied in any organ or lesions, as long as the patient or animal could be placed within the magnetic field, and the lesion deep-seated in body could be positioned at the focus site to localize systemically delivered cells/drugs to targeted site.

In conclusion, poor cell homing, retention and engraftment limit the efficacy of stem cell therapy. Our hypothesis might be a novel strategy worth to try to localize systemically delivered cells to targeted lesion which deep-seated in body, included the injured heart, subsequently enhance the efficacy of stem cell therapy.

Acknowledgement

This work was supported by National Natural Science Fundation of China (81000043, 81000105) and Research Fund for the Doctoral Program of Higher Education of China (20100071120072).

References

1. **Clifford DM, Fisher SA, Brunskill SJ, *et al.*** Stem cell treatment for acute myocardial infarction. *Cochrane Database Syst Rev*. 2012; 2: CD006536.
2. **Freyman T, Polin G, Osman H, *et al.*** A quantitative, randomized study evaluating three methods of mesenchymal stem cell delivery following myocardial infarction. *Eur Heart J*. 2006; 27: 1114–22.
3. **Hofmann M, Wollert KC, Meyer GP, *et al.*** Monitoring of bone marrow cell homing into the infarcted human myocardium. *Circulation*. 2005; 111: 2198–202.
4. **Penicka M, Widimsky P, Kobylka P, *et al.*** Images in cardiovascular medicine. Early tissue distribution of bone marrow mononuclear cells after transcoronary transplantation in a patient with acute myocardial infarction. *Circulation*. 2005; 112: e63–5.
5. **Li SH, Lai TY, Sun Z, *et al.*** Tracking cardiac engraftment and distribution of implanted bone marrow cells: comparing intra-aortic, intravenous, and intramyocardial delivery. *J Thorac Cardiovasc Surg*. 2009; 137: 1225–33. e1221.
6. **Chavakis E, Urbich C, Dimmeler S.** Homing and engraftment of progenitor cells: a prerequisite for cell therapy. *J Mol Cell Cardiol*. 2008; 45: 514–22.
7. **Singh JP.** Enabling technologies for homing and engraftment of cells for therapeutic applications. *JACC Cardiovasc Interv*. 2009; 2: 803–4.
8. **Rodriguez-Losada N, Garcia-Pinilla JM, Jimenez-Navarro MFGonzalez FJ.** Endothelial progenitor cells in cell-based therapy for cardiovascular disease. *Cell Mol Biol (Noisy-le-grand)*. 2008; 54: 11–23.
9. **Wu YZhao RC.** The role of chemokines in mesenchymal stem cell homing to myocardium. *Stem Cell Rev*. 2012; 8: 243–50.
10. **Langer R.** Drug delivery. Drugs on target. *Science*. 2001; 293: 58–9.
11. **Kim JA, Lee HJ, Kang HJPark TH.** The targeting of endothelial progenitor cells to a specific location within a microfluidic channel using magnetic nanoparticles. *Biomed Microdevices*. 2009; 11: 287–96.
12. **Pislaru SV, Harbuzariu A, Gulati R, *et al.*** Magnetically targeted endothelial cell localization in stented vessels. *J Am Coll Cardiol*. 2006; 48: 1839–45.
13. **Polyak B, Fishbein I, Chorny M, *et al.*** High field gradient targeting of magnetic nanoparticle-loaded endothelial cells to the surfaces of steel stents. *Proc Natl Acad Sci USA*. 2008; 105: 698–703.

14. **Darton NJ, Hallmark B, Han X, *et al.*** The in-flow capture of superparamagnetic nanoparticles for targeting therapeutics. *Nanomedicine*. 2008; 4: 19–29.
15. **Kobayashi T, Ochi M, Yanada S, *et al.*** A novel cell delivery system using magnetically labeled mesenchymal stem cells and an external magnetic device for clinical cartilage repair. *Arthroscopy*. 2008; 24: 69–76.
16. **Kobayashi T, Ochi M, Yanada S, *et al.*** Augmentation of degenerated human cartilage *in vitro* using magnetically labeled mesenchymal stem cells and an external magnetic device. *Arthroscopy*. 2009; 25: 1435–41.
17. **Sugioka T, Ochi M, Yasunaga Y, *et al.*** Accumulation of magnetically labeled rat mesenchymal stem cells using an external magnetic force, and their potential for bone regeneration. *J Biomed Mater Res A*. 2008; 85: 597–604.
18. **Wilhelm C, Bal L, Smirnov P, *et al.*** Magnetic control of vascular network formation with magnetically labeled endothelial progenitor cells. *Biomaterials*. 2007; 28: 3797–806.
19. **Cheng K, Li TS, Malliaras K, *et al.*** Magnetic targeting enhances engraftment and functional benefit of iron-labeled cardiosphere-derived cells in myocardial infarction. *Circ Res*. 2010; 106: 1570–81.
20. **Chaudeurge A, Wilhelm C, Chen-Tournoux A, *et al.*** Can magnetic targeting of magnetically labeled circulating cells optimize ntramyocardial cell retention? *Cell Transplant*. 2011; DOI: http://dx.doi.org/10.3727/096368911x612440.
21. **Cheng K, Malliaras K, Li TS, *et al.*** Magnetic enhancement of cell retention, engraftment and functional benefit after intracoronary delivery of cardiac-derived stem cells in a rat model of ischemia/reperfusion. *Cell Transplant*. 2012; DOI: http://dx.doi.org/10.3727/096368911x627381.
22. **Pei N, Huang ZY, Ge JBZheng WL.** *In vitro* study of deep capture of paramagnetic particle for targeting. *J Magn Magn Mater*. 2009; 321: 2911–5.
23. **Huang Z, Pei N, Wang Y, *et al.*** Deep magnetic capture of magnetically loaded cells for spatially targeted therapeutics. *Biomaterials*. 2010; 31: 2130–40.
24. **Forest VF, Tirouvanziam AM, Perigaud C, *et al.*** Cell distribution after intracoronary bone marrow stem cell delivery in damaged and undamaged myocardium: implications for clinical trials. *Stem Cell Res Ther*. 2010; 1: 4.