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

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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 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 chemotactant 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...
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 administrated intravenously into rats with myocardial infarction, meanwhile a spatially focusing magnetic field is adopted at the area of injured heart. As a result, systematically 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 route of cell delivery, offering the advantages of a non-surgical and non-interventional method that can be performed repeatedly. However, its 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.

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, and the lesion deep-seated in body could be positioned at the focus site to localize systemically delivered cells/drugs to targeted site.

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