TRPC6, a potential novel target for enhancing cardiac repair of bone marrow mesenchymal stem cells

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It has been well documented that bone marrow mesenchymal stem cells (BMSCs) therapy has been widely applied in ischemic diseases such as myocardial and hepatic ischemia, through promotion of angiogenesis and suppression of apoptosis [12]. Meanwhile, BMSCs transplantation has been demonstrated to be an effective therapy for cerebrovascular diseases, which could promote endogenous neurogenesis and behavioral recovery [3]. Previous studies have proved that the secretion of neurotrophins, such as nerve growth factor (NGF) and brain derived neurotrophic factor (BDNF), and their downstream signal pathways is important for understanding BMSCs transplantation in cerebral diseases [4–6]. In addition, BDNF modified BMSCs have also been employed to treat cerebral ischemic injury. They found that this therapy could effectively reduce the infarct size and improve the function of injured tissues [78]. Interestingly, a number of recent clinical studies have indicated that serum concentrations of BDNF and NGF were also deregulated in patients suffering from myocardial infarction [9–13]. Therefore, neurotrophins were indicated to play an important role in myocardial ischemia, which is probably contributable to BMSCs therapy.

Transient receptor potential canonical (subtype) 6 (TRPC6), a Ca2+-permeable nonselective cation channel, belongs to the mammalian transient receptor potential (TRP) family of ion channels [14,15]. Among them, TRPC subfamily consists of TRPC1, TRPC2, TRPC3/6/7 and TRPC4/5 [16]. TRPC6 channel has been shown to be expressed in various tissues and implicated in many different diseases, such as cardiac hypertrophy and cerebral ischemia [16,17]. Kuwahara et al. found that TRPC6 was a positive regulator of calcineurin-NFAT signaling pathway and also was a key component of a calcium-dependent regulatory loop which drives pathological cardiac remodeling. On the other hand, Du et al. uncovered that TRPC6 proteolysis could lead to ischemic neuronal cell death, and the repression of its degradation could preserve neuronal survival and prevent ischemic brain damage.

Based on the above findings, we proposed the hypothesis that neurotrophins may repair the ischemic myocardium via modulation of TRPC6 channel which might be one potential novel therapeutic target for myocardial infarction. Moreover, the plasma neurotrophins level may become a novel biomarker for the diagnosis of myocardial infarction. Our hypothesis is strongly supported by several following facts. First of all, the expression of TRPC6 protein was observed to be altered in ischemic diseases. It has been found that TRPC6 channel played a critical role in cerebral ischemia whereas other subtypes were unaltered [17]. Moreover, our previous bioinformatical results implied that TRPC6 may also be involved in MI [18]. Thus, experiments were conducted and confirmed that the level of TRPC6 indeed changed in ischemic myocardium [18]. Secondly, many studies have proved that BMSCs implantation is beneficial to brain and heart infarct, which could reduce the infarcted areas and induce reborn of neuron and cardiomyocyte, at least partly via secretion of neurotrophins [4–6]. Importantly, recent studies revealed that the protective effect of BMSCs is likely associated with the involvement of both neuronal and cardiac trophic factors, including BDNF, NGF and TRPC6 [19,20]. Meanwhile, it is confirmed that BDNF-TrkB could activate PLC which could regulate the activity of DAG and contribute to the activation of TRPC6 channel [21,22]. Taken together, it is believed that the potential mechanisms in this process may be relevant to BDNF-TrkB/NGF-TrkA signaling pathway, which regulated TRPC6 channel in the brain and further induces the activation of downstream survival molecules like extracellular regulated protein kinases (ERK) and calcium/calmodulin-dependent protein kinase (CAMK) [23].

In summary, the hypothesis is that employment of BMSCs in ischemic cardiomyopathy triggers the angiogenesis of injured heart through secretion of neurotrophins and regulation of TRPC6 channel. TRPC6 may serve as a potential target for the therapy of ischemic heart. We believe that stem cell therapy is correlated to amelioration of ischemic cardiomyocytes through secretion of neurotrophins. The pivotal role of TRPC6 in repairing injured tissues suggests its crucial involvement in the regeneration of MI. Of course, it needs further studies to prove it. If the hypothesis is true, agents regulating neurotrophins may also be effective for myocardial infarction patients in clinics. Once validated, TRPC6 may serve as a novel target in prevention and cure of MI.

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Correlations between myocardium selective videodensitometric perfusion parameters and corrected TIMI frame count in patients with normal epicardial coronary arteries

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TIMI frame count (TFC), was introduced in the early 1990s, as a method to assess the efficacy of thrombolysis and risk stratification in acute myocardial infarction (AMI) [1]. TFC proved to be a simple, reproducible, quantitative and objective method to evaluate epicardial flow not only in acute coronary syndrome settings, but in stable conditions with microvascular dysfunction, as well [2]. Recently, 2 different angiographic methods myocardial blush grade (MBG), and TIMI myocardial perfusion grading (TMP) have been described for direct assessment of myocardial perfusion in AMI [3]. However, these methods are limited inherently by their subjective nature and categorical values, and are not defined in stable patients. Alongside others novel computer-assisted videodensitometric methods have been introduced, which supply additional, objective and quantitative information on myocardial perfusion in AMI [4–6]. The objective of the present study was to evaluate regional myocardial perfusion assessed by our novel computerized videodensitometric method, and its relation to corrected TFC in non-AMI patients without epicardial coronary stenoses.

The current study comprised 43 patients with chest pain who had undergone elective coronary angiography with a negative result (<40% intraluminal coronary artery diameter stenosis) at

Table 1

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<th>Clinical, demographic and echocardiographic data of the patients.</th>
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Abbreviations. cTFC: corrected TIMI frame count, LAD: left anterior descending coronary artery, CX: left circumflex coronary artery, RC: right coronary artery.

References