GW23-e1565

ENHANCED HOMING OF MESENCHYMAL STEM CELLS TO THE ISCHAEMIC MYOCARDIUM BY ULTRASOUND-TARGETED MICROBUBBLE DESTRUCTION

doi:10.1136/heartjnl-2012-302920a.138

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Objectives The transplantation of bone-marrow derived mesenchymal stem cells (MSCs) to ischaemic myocardium is considered to be a useful therapeutic approach to ischaemic heart disease, but the MSCs delivery efficacy still can't meet the needs for therapy. Recently, ultrasound-targeted microbubble destruction (UTMD) has been utilised in the targeted delivery of stem cells. In this study, we tested the effects of myocardial micro-environment changes induced by ultrasound target microbubble destruction on promoting the MSCs homing to the ischaemic myocardium.

Methods In order to optimise the ultrasonic parameters and to explore the biological effects of different intensities of ultrasound mediated microbubble destruction to the myocardium of canine, 9 mongrel dogs were randomly divided into three groups. Three groups were treated with frequency of 1 MHz ultrasonic irradiation, but the intensity of ultrasonic irradiation was different in each group. Group 1 was treated with intensity of 0.5 W/cm^2, group 2 was treated with intensity of 1.0 W/cm^2 and group 3 was treated with intensity of 1.5 W/cm^2. The myocardium was harvested for hematoxylcne & eosin (HE) staining and Transmission electron microscope (TEM) detection to observe the tissue microstructures. The ultrasound parameters were optimised according to the results of TEM and HE staining results. Then, ultrasound with optimised parameters was used to investigate the cardiac microenvironment change induced by ultrasound mediated microbubble destruction. Twenty mongrel dogs were randomly divided into a treatment group and a control group after the establishment of animal models of myocardial infarction. One-week later, dogs in treatment group were treated by ultrasonic microbubble destruction for three times in 1 week, no treatment for the dogs in the control group. Vascular endothelial growth factor (VEGF), stromal cell-derived factor-1 (SDF-1), vascular cell adhesion molecule-1 (VCAM-1) and interleckin-1β (IL-1β) levels of the myocardium were measured by Real time PCR and western blot analyses in half of the dogs in each group after 2 weeks. The other half of the remaining dogs (n=10) in each group were transplanted with 5 ml DAPI labelled MSCs (2.45×10^7 cells/ml) with via coronary ostium by intervention technique under digital subtraction arteriography (DSA) monitor. Five-days later, the myocardium was harvested from the margin of the infarcted area. Laser scanning confocal microscope (LSCM) was used to observe the distribution of the stem cells.

Results The 1 MHz ultrasound at the intensity of 1.0 W/cm^2 provoked pertinent inflammatory reaction with mild myocardial damage. Real time PCR and western blot analyses showed that the expression of VEGF, SDF-1, VCAM-1 and IL-1β in the treatment group were much higher than that in the control group. By laser scanning confocal microscope, we found that the distribution of MSCs in pretreatment myocardium was significantly wider than that in the control group.

Conclusions Ultrasound targeted microbubble destruction improved myocardial microenviroment changes might promote MSCs homing to the ischaemic myocardium. This noninvasive technique might be a promising method for the cardiac cell transplantation therapy.