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Combined cord blood stem cells and gene therapy enhances angiogenesis and improves cardiac performance in mouse after acute myocardial infarction

H. K. Chen[*], H. F. Hung[*], K. G. Shyu[*†], B. W. Wang[*], J. R. Sheu[†], Y. J. Liang[*], C. C. Chang[*] and P. Kuan[*]

[*]Shin Kong Wu Ho-Su Memorial Hospital, [†]Taipei Medical University, Taipei, Taiwan

Abstract

Background Gene and stem cell therapies hold promise for the treatment of ischaemic cardiovascular disease. However, combined stem cell and angiogenic growth factor gene therapy for acute ischaemic myocardium has not been previously reported. This study hypothesized that combined stem cell and gene therapy would not only augment new vessels formation but also improve myocardial function in acute ischaemic myocardium.

Materials and methods Human angiopoietin-1 (Ang1) cDNA and $VEGF_{165}$ cDNA were ligated into AAV vector. The purified $CD34^+$ cells were obtained from human umbilical cord blood samples. Cord blood $CD34^+$ cells were transduced with AAV vector encoding either the human Ang1 (AAV-Ang1) or $VEGF_{165}$ (AAV-VEGF) cDNA alone, or both (AAV-Ang1 plus VEGF). Immediately after ligation of the left anterior descending coronary artery in male SCID mice, culture-expanded $CD34^+$ cells transduced with AAV-Ang1, AAV-VEGF or AAV-Ang1 plus VEGF were injected intramyocardially at the left anterior free wall.

Result Western blot showed that Ang1 and VEGF protein expressions were enhanced in the $CD34^+$cells transduced with AAV-Ang1 and AAV-VEGF, respectively. Infarct size significantly decreased and capillary density significantly increased after treatment with $CD34^+$/AAV-Ang1 plus VEGF when compared with treatment by $CD34^+$ only. Combined therapy with $CD34^+$ and AAV-Ang1, $CD34^+$ and AAV-VEGF, $CD34^+$ and AAV-Ang1 plus VEGF, all showed significantly higher cardiac performance in echocardiography than the therapy with $CD34^+$ alone 4 weeks after myocardial infarction.

Conclusions Combined therapy with human umbilical cord blood $CD34^+$ cells and both Ang1 and VEGF genes reduced infarct size, attenuated the progression of cardiac dysfunction and increased capillary density in acute myocardial infarction in mice.

Keywords Acute myocardial infarction, angiogenesis, angiopoietin-1, cell therapy, vascular endothelial growth factor, vasculogenesis.
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Introduction

Human umbilical cord blood contains a large amount of haematopoietic progenitors [1,2]. Angioblast-like endothelial progenitor cells (EPCs) can also be isolated from cord blood [3]. Umbilical cord blood appears to be a robust source for isolating EPCs and haematopoietic stem cells, and the EPCs derived from cord blood have a greater proliferative activity than those derived from adult peripheral blood [4]. Cord blood can be isolated noninvasively compared with adult bone marrow isolation. From these considerations, cord blood is a good source of stem cells for combining with gene transfer to achieve therapeutic angiogenesis.

Division of Cardiology (H. K. Chen, H. F. Hung, K. G. Shyu, P. Kuan) and Department of Education and Research (B. W. Wang, Y. J. Liang, C. C. Chang), Shin Kong Wu Ho-Su Memorial Hospital; Graduate Institute of Medical Sciences, College of Medicine, Taipei Medical University, (K. G. Shyu, J. R. Sheu), Taipei, Taiwan.

Correspondence to: Dr Kou-Gi Shyu, Division of Cardiology, Shin Kong Wu Ho-Su Memorial Hospital, 95 Wen-Chang Road, Taipei 111, Taiwan. Tel.: 886-2-28332211; fax: 886-2-28365775; e-mail: shyukg@ms12.hinet.net

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