Microfabricated biomimetic blood vessels for engineering functional cardiac patch

Teng Su [1,3]; Michael A. Daniele [1,2]; Ke Huang [1,3]; M. Taylor Hensley [1,3]; Ashlyn Young [1,2]; Junnan Tang [1,3]; Tyler Allen [1,3]; Adam Vandergriff [1,3]; Patrick Erb [1,2]; Frances S. Ligler [1]; Ke Cheng [1,3]

[1] Joint Department of Biomedical Engineering, University of North Carolina at Chapel Hill and North Carolina State University, [2] Department of Electrical and Computer Engineering, College of Engineering, [3] Molecular Biomedical Sciences, College of Veterinary Medicine, North Carolina State University

ke_cheng@ncsu.edu

Statement of Purpose: The cardiac patch strategy promotes heart regeneration after myocardial infarction (MI). One challenge is to create engineered tissues that can promote angiogenesis and anastomosis with host vasculatures after implantation [1]. In recent years, there has been an increasing interest in the design and fabrication of pre-vascularized tissue constructs that could promote angiogenesis and anastomosis after implantation [2]. In this work, we fabricated well-defined, biomimetic microvessels (BMVs) containing human umbilical vein endothelial cells (HUVECs) using a hydrodynamic focusing technique. BMVs mimic the natural architecture and functions of microvessels. A pre-vascularized cardiac stem cell patch (BMV-CSC patch) was subsequently created by embedding aligned BMVs in a fibrin gel matrix containing human cardiac stem cells (CSCs). We investigated the therapeutic benefits of the BMV-CSC patch in an immunodeficiency nude rat model of MI.

Methods: The BMV microfabrication process uses hydrodynamic focusing and *in situ* photopolymerization to incorporate HUVECs in the microvessel. The microvessels were composed of an interpenetrating network of poly (ethylene glycol) and gelatin methacrylamide. The biaxially aligned BMVs and CSCs were embedded into a fibrin gel. The mechanical properties of the patches were measured using a rotational rheometer. The microstructure of the patches was observed by a cryo-scanning electron microscope. Transplantation-ready tissue patches were obtained by cutting the fibrin gel into square pieces (5 mm × 5 mm × 1 mm). All animal procedures were approved by the North Carolina State University IACUC. The biocompatibility of the fibrin gel patch containing acellular microvessels was evaluated in immunocompetent normal rats. After that, therapeutic effects of cell-containing patches were evaluated in nude rats. Nude rats were randomized into 6 groups: 1) MI + BMV-CSC patch, 2) MI + patch containing randomly distributed HUVECs and CSCs, 3) MI + patch containing CSCs alone, 4) MI + empty patch, 5) MI only, and 6) a sham control with normal hearts. The left ventricular (LV) functions of the nude rats from all groups were assessed using echocardiography.

Results: The BMVs fabricated by microfluidic method employing hydrodynamic focusing supported cell attachment and proliferation. Subpopulation of HUVECs formed tubule-like morphology in the BMVs. The maturation of the HUVECs in the BMVs was confirmed by immunofluorescence and morphological analyses. The incorporation of the biaxially aligned microvessels significantly enhanced the stiffness of the fibrin gel matrix so that the BMV-CSC patches could be easily administrated *in vivo* by suturing. Patches containing acellular BMVs did not elicit any increased immune response in immunocompetent rats, showing excellent *in vivo* biocompatibility. After 4 weeks of implantation, the BMV-CSC patch-implanted group exhibited significantly augmented cardiac function with the highest ejection fraction (EF) compared to other patch-treated groups.

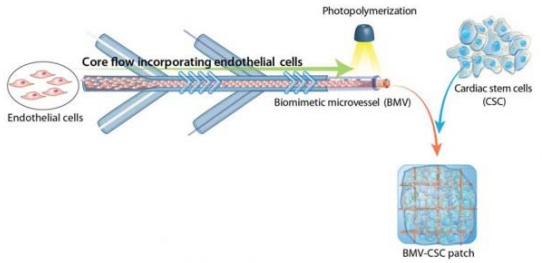

Figure 1. Schematic illustration of the fabrication of BMV-CSC cardiac patch.

Conclusions: The microengineered BMVs mimic the natural blood vessels by supporting the growth of human endothelial cells. They are promising for the creation of pre-vascularized tissue patches that can augment cardiac function and promote heart regeneration after MI.

Acknowledgments: This study was supported by a UNC General Assembly Research Opportunities Initiative award and National Institute of Health.

References:

1 Ogle BM *et al*. Sci. Transl. Med. 2016; 8: 342ps13.
2 Laschke MW *et al*. Biotechnol. Adv. 2016; 34: 112.