Combined Delivery of Self-assembling Peptide Nanofibers and Vascular Endothelial Growth Factor (VEGF) Creates An Intramyocardial Microenvironment for Post-infarction Neovascularization

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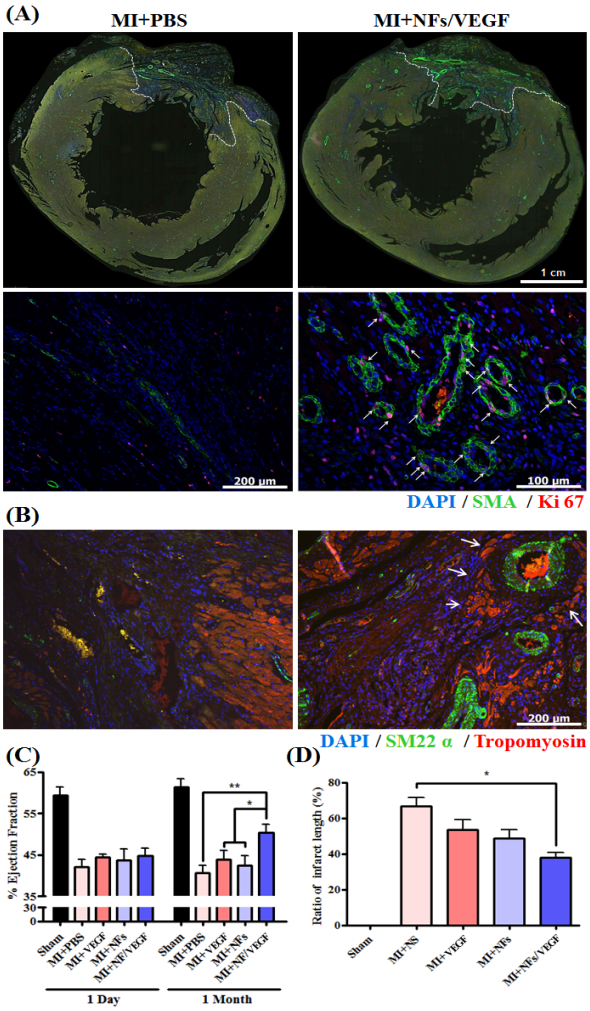
Introduction: Congestive heart failure is the top killer in developed countries, and the predominant cause is myocardial infarction (MI) due to blockage of coronary circulation. Therefore, therapies improving myocardial neovascularization may be a promising approach to ameliorate cardiac function after MI. Vascular endothelial growth factor (VEGF) is one of the well-known angiogenesis factors; however, effective angiogenesis is determined by precise control of microenvironmental concentration, which might also be a major reason for failed clinical trial results[1]. Moreover, bone marrow circulating cells or endothelial progenitor cells may be recruited by VEGF signal to enhance angiogenesis and achieve further asteriogenesis[2]. Therefore, how to retain these cells *in situ* would be another challenge to successful neovascularization.

Methods: Self-assembling peptide nanofibers (NFs) were demonstrated to create an intramyocardial microenvironment for endothelial cell infiltration *in vivo*[3]. Accordingly, we hypothesized that combined delivery of NFs with VEGF may create an intramyocardial microenvironment with prolonged VEGF releasing to improve post-infarction neovascularization in rats. Experimental MI was created by a permanent ligation of left anterior descending coronary artery, immediately followed with injection of 100 µl of 100 ng/ml $VEGF_{165}$, with or without NF, into the border and infarcted zones (n≥8 in each group of sham, MI+PBS, MI+NFs, MI+VEGF, MI+NFs/VEGF).

Results: Out results showed that delivery of VEGF along with NFs prolonged the VEGF releasing for up to 14 days *in vivo*, and the injection of NFs/VEGF significantly increased capillary and artery density at 28 days after MI (2.8 and 4.4 fold compared to MI+PBS, respectively, data not shown). The smooth muscle cells of the arteries were co-stain with $Ki67^+$, indicating the cells were regenerating rather than being protected (Fig. A). On the other hand, the cardiomyocytes at the border region was protected by these regenerating vessels (Fig. B), and thus the myocardial function (40.6% for MI+PBS and 50.4% for MI+NFs/VEGF, Fig C) was improved and pathological remodeling was prevented at 28 days after MI (66.5% for MI+PBS and 38.1 for MI+NFs/VEGF, Fig D).

Summary: We demonstrate that combined delivery of NFs with VEGF creates an intramyocardial microenvironment for neovascularization, and thus protects cardiac function after MI. Future studies will be carried out to explore the mechanisms and to translate this approach into a clinical therapy for patients.



Figures. Intramyocardial NFs/VEGF injection promotes post-infarction neovascularization and thus cardiac function. (A) At 14 days after MI, the border and infarct areas were indicated as dot line at upper panel and magnified at lower panel, wherein $Ki67^+/SMA^+$ cells, which indicates regenerating smooth muscle cells, were arrowed. (B) At 28 days after MI, cardiomyocytes were protected by arteries at peri-infarct area after NFs/VEGF treatment. (C) NFs/VEGF injection improves cardiac systolic function at 28 days after MI. (D) NFs/VEGF injection reduces infarct size at 28 days after MI.

Reference:

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