Rapid Improvement in Myocardial Infarction Therapy by Application of an Injectable Tissue Engineered Nanoscaffold

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Statement of Purpose Recently, cardiomyocyte transplantation has attracted much attention in the research field of cardiovascular surgery as a next-generation therapy for the majority of patients with end-stage heart failure because of the shortage of donor hearts for cardiac transplantation. In North America, for instance, fewer than 20% of transplantation candidates receive donor hearts. Several research groups have reported that the transplantation of cardiomyocyte or non-cardiomyocyte cells, such as skeletal myoblasts, on mesenchymal stem cells, was effective to improve the left ventricular (LV) function in rat myocardial infarction models [1]. However, there are several problems for cell transplantation, such as poor supply of oxygen and nutrients to the cell transplanted and the source of donor cells. To improve the *in vivo* environment of transplanted cells, it is promising to induce in advance angiogenesis around the transplanted site by any means. This blood supply will enable the transplanted cells to prolong survival and maintain cell functions. The objective of the present study is to fabricate the 3-D networks of nanofibers by mixing basic fibroblast growth factor (bFGF) suspension with aqueous solution of peptide amphiphile and used it for feasibility of prevascularization by the bFGF release from the 3-D networks of nanofibers in improving efficency of cardiomyocytes trasplatation in a rat ischemeic cardiomyopathy model.

Methods: We demonstrate that a 3-D scaffold can be formed by mixing of peptide-amphiphile (PA) aqueous solution with bFGF suspension. PA was synthesized by standard solid phase chemistry that ends with the alkylation of the NH_2 terminus of the peptide. *In vitro* release profile of bFGF from 3-D scaffold of PA was investigated while angiogenesis induced by the released bFGF was assessed. When aqueous solution of PA was subcutaneously injected together with bFGF suspension into the back of rats, a transparent 3-D hydrogel was formed at the injected site and induced significant angiogenesis around the injected site, in marked contrast to bFGF injection alone or PA injection alone. Rats with myocardial infarction received the intramuscular injection of culture medium (Control), or that containing fetal cardiomyocytes (TX) or PA incorporating bFGF, and PA incorporating bFGF plus fetal cardiomyocytes 1 week later (FGF-TX). The left ventricle (LV) function of rat hearts was assessed by echocardiography and cardiac catheterization 4 weeks later.

Results and Discussion

SEM photograph of nanofibers formed through self assembly of PA revealed the formation of fibrous assemblies of nanofibers with an extremely high aspect ratio, and high surface areas, 20 to 30 nm in diameter and with lengths of hundreds of nanometers to a few micrometers.

Four weeks after transplantation of fluorescent-labeled cardiomyocytes, many fluorescent positive cells were detected in the scar area. Whereas most of the transplanted cells were found around peri-infraction regions in the TX group, transplanted cells in the FGF-TX group were detected in all the scar areas including infract regions, even in the middle of the scar [2]. The infract LV wall was thicker in the FGF-TX group than in the control group (Fig. 2 A-B).

(A) (B)

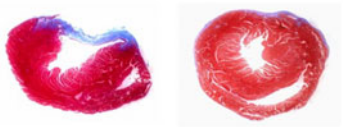

Figure 2: Histological findings 4 weeks after each treatment are shown. A, control group; B, FGF-TX group (hematoxylin and eosin staining; original magnification: x 1).

Conclusions

The bFGF incorporated PA developed in this study were found to be useful for prolonged growth factor release. This study was designed to improve the efficacy of fetal cardiomyocyte transplantation by prevascularization in a rat ischemic cardiomyopathy model through the controlled release of bFGF from bFGF-incorporated 3-D scaffold of PA. These results strongly suggest that the angiogenesis in advance induced by the controlled release of bFGF from bFGF-incorporated PA played an important role in creating an environment suitable for the survival and activity of transplanted cells for further applications in tissue regeneration.

References

1. Sakai T et al. J Thorac Cardiovasc Surg 1999; 118:715-725.