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Cardiac patch loading MSCs overexpressing TÃÂ²4 promotes repair of the infarcted myocardium by endogenous regenerative mechanisms

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Recent studies suggest that the epicardium plays an important role in cardiomyogenesis during development, while it becomes quiescent in adult heart. Thymosin beta 4 (Tβ4) has an effect on activating the epicardium. However, effectiveness of Tβ4 administration is unsatisfactory. Therefore, this study prepared cardiac patch and investigated efficiency of activating the epicardium by Tβ4 released sustainedly from the cardiac patch. Mesenchymal stem cells (MSCs) isolated from bone marrow of rats and mice were transfected with Tβ4. Tβ4 release from the cells was determined with an acquity ultra-performance liquid chromatography system. For preparing of cardiac patch, the cells transfected with Tβ4 and Flag were seeded on PLACL/collagen membrane formulated by electrospinning. The survival and proliferation of the cells on the nanofibers were examined after treatment with hypoxia. In MI models of rats and Wt1CreERT2/+, R26mTmG mice, the patches were implanted on the epicardium of the infarcted region. In rat models, differentiation of the epicardium-derived cells (EPDCs) and the engrafted MSCs towards cardiomyocytes and vascular cells was examined by Wt1 immunostaining and Flag labeling. In transgenic mouse models, the activated EPDCs expressed GFP. At four week after implantation of the patches, cardiac function was improved significantly, scar area in the infarcted region was reduced obviously. EPDCs increased in subepicardium and myocardium, and some Wt1+ cells and GFP+ cells expressed CD31, α-SMA or cTnT. Moreover, c-kit+ cells were observed in subepicardium and myocardium, and a few of them expressed CD31, α-SMA or cTnT. Flag labeling showed that some engrafted MSCs migrated into subepicardium and myocardium. These results suggest that Tβ4 released from the transfected MSCs in PLACL/collagen nanofibrous patches may effectively attenuate left ventricular remodeling and improve cardiac function by activating the epicardial cells and recruiting endogenous stem cells. Our finding provides a novel strategy for myocardial regeneration by enhancing the endogenous regenerative mechanisms. References: 1. Guo H D, Cui G H, Wang H J and Tan Y Z (2010) Transplantation of marrow-derived cardiac stem cells carried in designer self-assembling peptide nanofibers improves cardiac function after myocardial infarction. Biochem Bioph Res Co. 399:42–8. 2. Guo H D, Wang H J, Tan Y Z and Wu J H (2011) Transplantation of marrow-derived cardiac stem cells carried in fibrin improves cardiac function after myocardial infarction. Tissue Eng Part A 17:45–58. 3. Kai D, Wang Q L, Wang H J, Prabhakaran M P, Zhang Y Z, Tan Y Z and Ramakrishna S (2014) Stem cell loaded nanofibrous patch promotes regeneration of infarcted myocardium with functional improvement in rat model. Acta Biomaterialia. 10:2727–38. 4. Wang Q L, Wang H J, Li Z H, Wang Y L, Wu X P, Tan Y Z (2017) Mesenchymal stem cell-loaded cardiac patch promotes epicardial activation and repair of the infarcted myocardium.

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