BIOENGINEERING

Injectable hydrogel with MSNs/microRNA-21-5p delivery enables both immunomodification and enhanced angiogenesis for myocardial infarction therapy in pigs

Yan Li[1,2]*, Xin Chen[3]*, Ronghua Jin[3], Lu Chen[1], Ming Dang[4], Hao Cao[5], Yun Dong[5], Bolei Cai[2], Guo Bai[1], J. Justin Gooding[6], Shiyu Liu[7], Duohong Zou[1†], Zhiyuan Zhang[1†], Chi Yang[1†]

Current therapeutic strategies such as angiogenic therapy and anti-inflammatory therapy for treating myocardial infarction have limited success. An effective approach may benefit from resolution of excessive inflammation combined with enhancement of angiogenesis. Here, we developed a microRNA-21-5p delivery system using functionalized mesoporous silica nanoparticles (MSNs) with additional intrinsic therapeutic effects. These nanocarriers were encapsulated into an injectable hydrogel matrix (Gel@MSN/miR-21-5p) to enable controlled on-demand microRNA-21 delivery triggered by the local acidic microenvironment. In a porcine model of myocardial infarction, we demonstrated that the released MSN complexes notably inhibited the inflammatory response by inhibiting the polarization of M1 macrophage within the infarcted myocardium, while further microRNA-21-5p delivery by MSNs to endothelial cells markedly promoted local neovascularization and rescued at-risk cardiomyocytes. The synergy of anti-inflammatory and proangiogenic effects effectively reduced infarct size in a porcine model of myocardial infarction.

INTRODUCTION

Myocardial infarction (MI) remains one of the leading causes of death worldwide. The inflammatory response caused by MI sets the stage for fibrous tissue and often progresses to chronic heart failure (*1*), resulting in a more than 50% 5-year mortality after MI (*2*). An immunomodulation strategy, which prevents an excessive inflammatory response, can be beneficial to reduce scar tissue formation. Immunomodulation alone can likely prevent ongoing damage but fails to restore the compromised heart function. Promoting angiogenesis in the infarct area has the potential to reperfuse and salvage the surviving ischemic myocardium (*3*). Therefore, we hypothesize that long-term improvements in heart function after MI can be achieved by the combination of resolving inflammation and promoting angiogenesis in the infarct area.

Various therapeutics, such as cell transplant, exosomes, and nucleic acids, have been explored to treat MI and restore cardiac function, with varying degrees of success. Cell transplantation could enhance the functions of the infarcted heart (*4*), but only cardiomyocytes derived from pluripotent stem cells have been shown to engraft and generate functional myocardium (*5*). Limitations in cell sources, potential immune responses, and rigorous regulations hinder the clinical translation of cell-based therapies. Several studies have shown that cell-derived exosomes may be effective in treating cardiovascular diseases (*6*). However, there are obvious variations in exosomes resulting from multiple factors such as cell phenotype, preparation procedure, and exosome storage conditions (*7*). MicroRNAs (miRNA) are appealing genetic tools to stimulate cardiac performance, as they could regulate the levels of multiple genes simultaneously. Recently, it has been suggested that the cardiovascular system is regulated via a miRNA network (*8*). High-throughput screening work revealed that miRNAs, particularly microRNA-21-5p (miR-21-5p), are highly expressed in endothelial cells and stimulate angiogenesis by targeting antiangiogenic genes (*9*). miRNAs have a unique capacity to simultaneously promote the secretion of multiple endogenous molecules that might enhance vessel regeneration in the ischemic tissue. Negatively charged miRNAs typically cannot cross the cell membrane without a transfection agent. In addition, miRNAs are relatively unstable and can be degraded rapidly in vivo (*10*). Thus, vectors that protect and deliver miRNAs into cells are crucial to improve the efficacy of miRNA therapy.

Mesoporous silica nanoparticles (MSNs) have been developed as a promising vector for miRNA delivery because of their many excellent properties, such as good biocompatibility and high transfection efficiency. Moreover, studies have shown that inflammation can be modulated by phagocytosis of micro/nanomaterials, such as liposomes (*11*), polymer particles (*12*, *13*), and inorganic particles (*14*). Macrophages play a central role in regulating infarct-induced inflammation because they adopt proinflammatory (M1) phenotypes. In this study, we found that MSNs showed great potential in inhibiting

[1]National Clinical Research Center for Oral Diseases; Shanghai Key Laboratory of Stomatology and Shanghai Research Institute of Stomatology, Department of Oral Surgery, Shanghai Ninth People's Hospital, College of Stomatology, Shanghai Jiao Tong University School of Medicine, Shanghai 200011, China. [2]State Key Laboratory of Military Stomatology and National Clinical Research Center for Oral Diseases and Shaanxi Key Laboratory of Oral Diseases, Department of Prosthodontics, School of Stomatology, The Fourth Military Medical University, Xi'an 710032, China. [3]School of Chemical Engineering and Technology, Shaanxi Key Laboratory of Energy Chemical Process Intensification, Institute of Polymer Science in Chemical Engineering, Xi'an Jiao Tong University, Xi'an 710049, China. [4]School of Dentistry, University of Michigan, Ann Arbor, MI 48109, USA. [5]Department of Cardiac Surgery, Shanghai East Hospital, Tongji University School of Medicine, Shanghai 200120, China. [6]School of Chemistry, Australian Centre for NanoMedicine and ARC Australian, Centre of Excellence in Convergent Bio-Nano Science and Technology, University of New South Wales, Sydney 2052, Australia. [7]Key Laboratory of Military Stomatology and National Clinical Research Center for Oral Diseases and Shaanxi Key Laboratory of Oral Diseases, Center for Tissue Engineering, School of Stomatology, The Fourth Military Medical University, Xi'an, Shaanxi 710032, China.
*These authors contributed equally to this work.
†Corresponding author. Email: yangchi63@hotmail.com (C.Y.); zhzhy0502@163.com (Z.Z.); zdhyy@ahmu.edu.cn (D.Z.)