Therapeutic potentials of miRNA-21 regulation by peripheral blood derived-exosomes in myocardial infarction

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**Introduction :** Myocardial infarction (MI) is a public health problem and a leading cause of mortality globally. Due to insufficient current treatments, it is essential to develop effective alternatives for treating MI. Recently, microRNAs (miRNAs), a class of small non-coding RNAs that control gene expression of targeted mRNAs, have been explored in treating cardiac diseases. However, insufficient stability and poor cellular uptake in vivo restrict miRNAs' clinical application. Lately, exosomes have emerged as a promising drug delivery system with high therapeutic efficacy, but quantity may constitute major issues. As human peripheral blood is easily obtained, the use of human peripheral blood-derived exosomes as a miRNAs delivery system, has substantial potential as a therapeutic tool. Thus, this study investigated miRNA-21 regulation by human peripheral blood-derived exosomes may provide as an effective regulator for the treatment of MI.

**Methods :** We conducted a bioinformatics analysis and performed luciferase assay to confirm whether a direct target of miRNA-21 or not. To devise an effective strategy for clinical application with therapeutic miRNAs, we isolated exosomes from human peripheral blood using the Exoquick exosome precipitation kit (System Biosciences, Palo Alto, CA, USA). Transmission electron microscopy (TEM), nanoparticle trafficking analysis (NTA) and western blotting were used to characterize the isolated exosomes. We then assessed the uptake and distribution of exosomes in vivo. For experimental mouse MI, the left anterior descending (LAD) artery ligation was done with a 6-0 silk suture.

**Result :** The detection of morphology, size distribution and protein markers of typical exosomes indicated that the exosomes were successfully isolated from human peripheral blood. The PKH26 fluorescence became concentrated in the heart, observed using an in vivo imaging system (IVIS). In addition, PKH26-labeled exosomes co-localized with cTnI+ cells, suggesting an efficient in vivo uptake of the exosomes by cardiomyocytes. After validating our exosomes platform's potential utility in vivo, we evaluated whether miRNA-21 regulation by exosomes led to cardiac function recovery after MI. Mice treated with anti-miRNA-21-loaded exosomes significantly reduced infarct size (p<0.001), and improved survival rate with the augmentation of cardiac function as measured by echocardiography. In contrast, mice treated with miRNA-21-loaded exosomes completely reversed the effect of anti-miRNA-21-loaded exosomes.

**Conclusion :** In this study, we suggest that human peripheral blood-derived exosomes function as efficient vehicles for the delivery of miRNAs, which in turn may potentially be used for the treatment of MI. Furthermore, our results show that anti-miRNA-21 exerts a cardioprotective effect through targeting novel genes, making them potential pharmacological candidates for MI treatment.