Exploring Synergistic Effects of Transient OSKM Factors and pro-proliferative miR-199a-3p using mRNA-LNP for Cardiac Regeneration

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Background: In mammals, neonatal cardiomyocytes retain the ability to regenerate. However, this regenerative capacity rapidly ceases within a few days after birth. Consequently, after myocardial infarction (MI), cardiac damage is repaired through fibrotic scarring and residual cardiomyocyte hypertrophy, commonly leading to heart failure. To promote cardiac repair, our group has previously identified several pro-proliferative microRNAs (miRNAs), including hsa-miR-199a-3p, that are very effective at inducing endogenous cardiomyocyte proliferation and improving cardiac function. Here, we wanted to improve the efficiency of miRNA-stimulated cardiac regeneration. Method & Results: We tested whether transiently reprogramming adult cardiomyocytes towards a neonatal/embryoniclike state by delivering the mRNAs coding for the Yamanaka factors (OSKM) renders these cells more permissive to the effects of pro-regenerative miR-199a-3p. First, we evaluated this strategy in neonatal cardiomyocytes. We co-transfected OSKM mRNAs and miR-199a-3p and assessed proliferation by EdU incorporation. We found that co-transfection significantly increased the proportion of proliferating cells as well as increased cardiomyocyte nuclei number compared to miR-199a-3p alone. Next, we investigated whether this enhanced proliferative response could also be achieved in the adult murine hearts. For this purpose, we co-administered OSKM factors and miR-199a-3p using a cardiomyocytespecific lipid nanoparticle via intracardiac injection in the infarct border zone. We found that administration of either OSKM or miR-199a-3p alone as well as OSKM plus miR-199a-3p increased cardiomyocyte proliferation in mouse hearts 8 days post MI compared to fluc controls. Conclusion: These findings support the potential of transient partial reprograming as a strategy to enhance miRNAmediated endogenous cardiac regeneration.