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Cardiovascular diseases are the major cause of death globally. They include ischemic heart disease as a consequence of myocardial infarction. During an infarct, billions of cardiomyocytes irreversibly die, replaced by non-contractile fibrotic tissue. Among the approaches under investigation for cardiac regeneration, the release of specific microRNAs (miRNAs) to the infarcted area has been reported to promote cardiomyocyte proliferation or the direct reprogramming of cardiac fibroblasts (CFs) into induced cardiomyocytes (iCMs). Our group has recently demonstrated that a combination of four miRNAs called miRcombo (miR-1, 133, 208, 499), previously identified by others in mouse model, can trigger trans-differentiation of human CFs into iCMs. CFs were transfected with miRcombo using a commercially available agent and then cultured up to 30 days. After 2 weeks culture time, 11% of the cells expressed cardiac troponin T (cTnT), while after 4 weeks culture time, 38% of the cells showed spontaneous calcium transients. Subsequently, new lipoplexes based on a mixture of cationic and helper lipids were formulated for efficient encapsulation and delivery of microRNAs to human CFs, aimed at enhancing direct reprogramming efficiency. Lipoplexes loaded with one microRNA (negmiR or miR-1) were initially prepared showing 99% encapsulation efficiency and an average hydrodynamic diameter increasing from 372 nm to 876 nm and a Z-potential decreasing from + 40 mV to -26 mV with decreasing N:P ratios (3.0-0.35). Based on physicochemical characteristics and stability experiments at different temperatures (4°C and 37°C), lipoplexes with a N:P ratio of 3 were selected for further *in vitro* tests with human CFs, showing biocompatibility and significantly higher miR-1 expression, compared to a commercial agent. Encapsulation of miRcombo within the new lipoplexes is in progress with the aim to validate the nanocarriers as efficient vectors for direct cardiac reprogramming.

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