Effective cardiac mRNA delivery using lipid nanoparticles

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Background/Introduction: Heart failure is a global health burden for which there is no curative treatment available that aims to recover the impaired cardiac function.(1) Messenger RNA (mRNA) has emerged as a promising tool for protein replacement therapy. Endogenous mechanisms that enable repairing the heart can potentially be triggered by cardiac messenger RNA (mRNA) delivery.(2,3) Furthermore, the mRNA molecule can be modified in its secondary structure in order to reduce its immunogenicity and susceptibility to degradation by RNases. Clinical application of modified mRNA (modRNA) is challenged by the lack of effective and safe delivery systems. Lipid nanoparticles (LNPs) represent a well-characterized class of mRNA delivery systems, which were recently approved for clinical usage in mRNA-based covid-19 vaccines.

Purpose: We compared cardiac delivery efficiency between different mRNA-LNPs formulations and naked mRNA in citrate buffer upon intramyocardial administration in mice. Furthermore, we aimed to identify cardiac cell types that were targeted. Finally, we assessed whether LNP administration induces a local immunogenic response.

Methods: Different LNP formulations were tested in vitro and in vivo for luciferase or GFP – encoding modRNA delivery. In vitro, LNP mediated modRNA delivery was assessed in human endothelial cells (HMEC-1), induced pluripotent stem cell-derived cardiomyocytes (iPS-CMs) and induced pluripotent stem cell-derived fibroblasts (iPS-FBs). In vivo, mice undergoing open chest heart surgery under general anaesthesia were intramyocardially injected with 2.5μg modRNA in LNPs or in citrate buffer. In order to quantify tissue distribution of mRNA delivery levels, luciferase expression was measured in various organs 24h after administration. Moreover, to identify cellular uptake specificity, histology was performed on mice treated with GFP modRNA.

Results: mRNA-LNPs outperformed naked mRNA upon intramyocardial administration in mice (figure 1 a, d-i). Although LNPs were mainly in the injection site in the left ventricular wall (Figure 1 b), the liver showed to be the main mRNA-LNP target organ (figure 1 a, b). mRNA-LNPs showed targeting of epicardial and interstitial cardiac cells (figure 1 c). Among the tested C12-200 LNP formulations, no differences in in vivo delivery efficiency were observed (Figure 1 a, d). Most importantly, variations on the ionizable lipid LNP component determined the LNP local immune response.

Conclusion(s): We present a proof of concept of a promising strategy for delivering mRNA to the heart by using LNPs as delivery systems, which proved to be more efficient than the current state of the art (mRNA in citrate buffer). LNP optimization to better target the heart could introduce a novel approach to achieve cardiac tissue repair.