Title: Hybrid nanoparticles for targeted microRNA delivery to cardiomyocytes

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Abstract Body

Introduction: Myocardial infarction (MI) is the main cause of death worldwide, inducing the irreversible loss of cardiomyocytes (CMs) in humans, which leads to heart failure. CM proliferative ability has been observed only in newborn mammals (mice, pigs), while little or no proliferative capacity has been observed in humans (1). The induction of CMs endogenous proliferation after injury may represent a potential approach to induce cardiac regeneration and restore its functions (2). Previous studies have reported neonatal and adult CMs proliferation through viral-mediated expression of exogenous microRNAs (miRNAs), such as miR-199-3p, which is able to induce the re-entering of CMs into the cell cycle (2). In delivering miRNAs, nanocarriers emerge as a safer and more effective alternative to viral vectors, especially concerning future clinical applications (3). Hence, CM-targeted nanocarriers are under development. In this work, we designed novel hybrid nanoparticles (H-NPs) providing high miRNA encapsulation ability and stability in physiological conditions. Furthermore, their surface functionalization (F_H-NPs) with a specific ligand enabled selective CMs targeting.

Methods: H-NPs, loaded with miR-199-3p or control miRNA, were formulated and physico-chemically characterized. Surface functionalization (F_H-NPs) was performed using a cardiac specific peptide. H9c2 cell line was used to assess cytocompatibility, miRNA uptake, and transfection efficiency upon treatment with both nanoparticles.

Results: H-NPs/miRNA and F_H-NPs/miRNA showed an average hydrodynamic diameter of nearly 200 nm, a negative Z-potential, high miRNA encapsulation (99 %), controlled release over time, and long-term stability during storage. Additionally, nanoparticles displayed high cytocompatibility and efficient uptake by H9c2 cells, inducing significant mRNA target downregulation. Notably, F_H-NPs exhibited superior internalization in H9c2 cells compared to H-NPs.

Conclusion: F_H-NPs/miRNA demonstrated remarkable cytocompatibility, stability in physiological conditions, and efficient transfection of H9c2 cells. Hence, they are promising as nanocarriers for precise delivery of therapeutic miRNAs to target CMs, deserving further investigations.

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Presenter biography: Martina Coletto is a PhD student in Bioengineering and Medical-Surgical Science at Politecnico di Torino. She obtained a master's degree in Biomedical Engineering from the same institution. Her research focuses on cardiac tissue engineering, nanomedicine, and RNA-based therapy.

Learning Objectives

Understand the potential of active targeting to improve the delivery of microRNA-based therapies.