Abstract: 3072

Myocardial delivery of therapeutic miR-133 via inhalable nanoparticles prevents the pathologic development in a model of ventricular pressure overload

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Background
MicroRNAs (miRs) are regulators involved in several biological processes and have been recognized as potential novel therapeutic targets for the treatment and prevention of CDs. We previously demonstrated that the cardiac-enriched miR-133, which is inversely related to failing heart conditions, is involved in several aspects of pathological cardiac remodeling via mitigation of cardiac hypertrophy and fibrosis, fine-tuning of the β1-adrenergic receptor signaling, and protection against oxidative stress-mediated apoptosis. However, effective and clinically oriented interventions aiming to delivery exogenous miR-133 for preventing the stress-induced downregulation of miR-133 levels are still missing.

Here, we applied an unconventional and effective nanotechnology-based inhalation approach enabling the delivery to diseased heart of exogenous miR-133 loaded into biocompatible and biodegradable calcium phosphate-based nanoparticles (CaPs).

Methods
Male C57Bl/6J mice (8 weeks) were subjected to a trans-aortic constriction (TAC), to induce a ventricular pressure overload. 4 experimental groups of TAC animals were randomly assigned to different intratracheal administrations of: 1. Saline (TAC Control); 2. CaP-miR133 (TAC CaP-miR133); 3. Pristine miR-133 (TAC miR133); 4. Unloaded CaPs (TAC CaP). Not TAC operated mice served as SHAM group. Intratracheal nebulizations were performed immediately after TAC surgery once-a-day in alternative days for 4 consecutive weeks. Echocardiography (ECO) were conducted before TAC, at 2 and 4 weeks after surgery. ECO as well as molecular and histological analyses were performed at sacrifices.

Results
ECO analyses showed an effective CaP-miR133-associated reversal of the failure progression, preserving left ventricular internal diameter (LVID) during cardiac cycle, ejection fraction (EF) and fraction shortening (FS), both at 2 and 4 weeks after TAC. This improvement was associated with the restoration of physiological levels of miR-133 in TAC-stressed isolated cardiomyocytes as well as its contractile activity. TAC mice receiving CaP-mir133 showed reduced indexes of fibrosis. In contrast, no beneficial effects were observed when unloaded CaPs or pristine miR-133 were administered. No major alterations of the immunological status of mice were observed after CaP-miR133 administration.

Conclusions
Intratracheal nebulization of miR-133-loaded nanoparticles is an effective approach for the beneficial restoration
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Conclusions

Intratracheal nebulization of miR-133-loaded nanoparticles is an effective approach for the beneficial restoration of cardiac performance, cell contractility and remodeling in a mouse model of left ventricular pressure overload. Providing the evidence for a potential innovative application of the emerging nanotechnologies, our approach might represent an important step forward for the treatment of cardiovascular diseases.