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Biofunctional lipid delivery system for reversing vascular remodeling in pulmonary arterial hypertension

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1. Introduction

Pulmonary arterial smooth muscle cells (PASMCs) display a hyperproliferative, apoptosis-resistant phenotype, which is promoted by endoplasmic reticulum (ER) stress and mitochondrial calcium uniporter (MCU) dysfunction, is a key driver of the vessel remodeling in pulmonary arterial hypertension (PAH)[1, 2]. Inducing PASMCs apoptosis through synergistic modulation of the ER-mitochondria to reverse vascular remodeling would be an effective therapeutic strategy for PAH. However, the precise therapeutics delivery to pulmonary artery presents a significant challenge due to the persistent hemodynamic shear stress and relatively high blood flow velocity，let alone to endoplasmic reticulum of PASMCs

2. Methods

Inspired by the specific homing mechanisms of various cells in organisms, we constructed a biofunctional lipid delivery system (BLDS) including ER stress inhibitor 4-phenylbutyric acid (4-PBA) loaded neutrophil membrane (NEM)-incorporated liposomes (4-PBA Lips@NEM) and miRNA 138-5P inhibitor loaded bioinspired LNP (miR LNP@NEM) (Fig.1). The incorporation of neutrophil membrane endowed nanoparticles with both inflammatory and ER targeting ability, which were confirmed in inflammatory endothelial cells (ECs) and PAH PASMCs. Thereafter, we validated the pro-apoptotic effect of BLDS by attenuating ER stress and restoring MCU expression in vitro. Last, we evaluated the therapeutic effect of the biomimetic system in monocrotaline (MCT)-induced PAH rat model

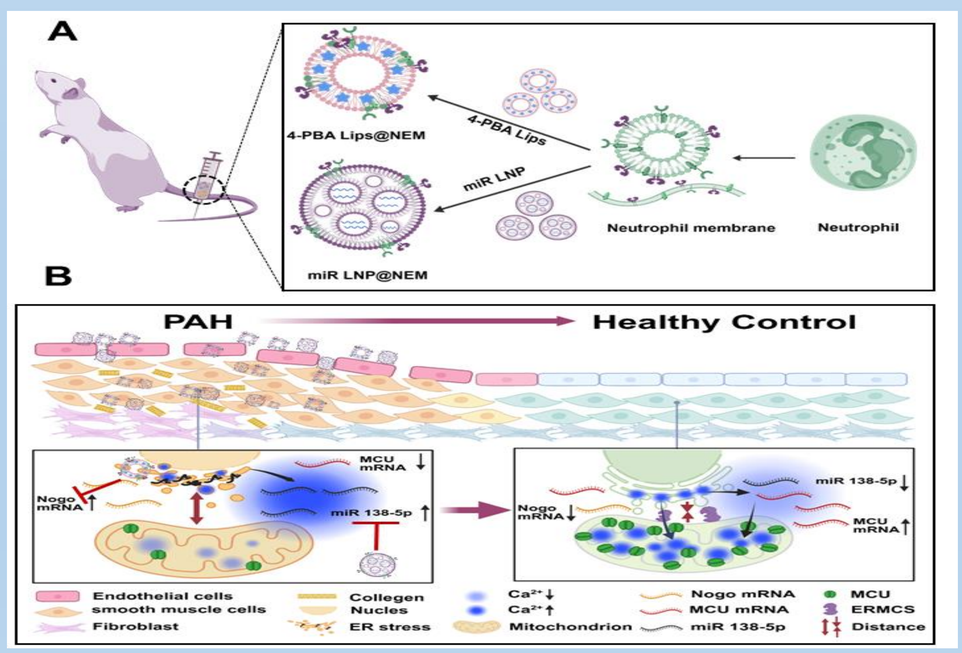

Fig1. (A) Procedure of the preparation of co-delivery biomimetic system. (B) After intravenous injection, the nanoparticles were precisely delivered into PA due to the specific binding of CXCR4 expressed on NEM and CXCL12 presented on inflammatory vascular endothelial cells, then penetrated across EC barrier to media and taken up by PASMCs. Meanwhile, 4-PBA released from 4-PBA Lips@NEM in ER to attenuate ER stress and down-regulate Nogo expression. miR 138-5p released from miR LNP@NEM in cytoplasm to restore MCU expression. The two facilitated Ca^{2+} entry into the mitochondrial matrix, which triggered PASMC apoptosis eventually.

Acknowledgements

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3. Results and Discussions

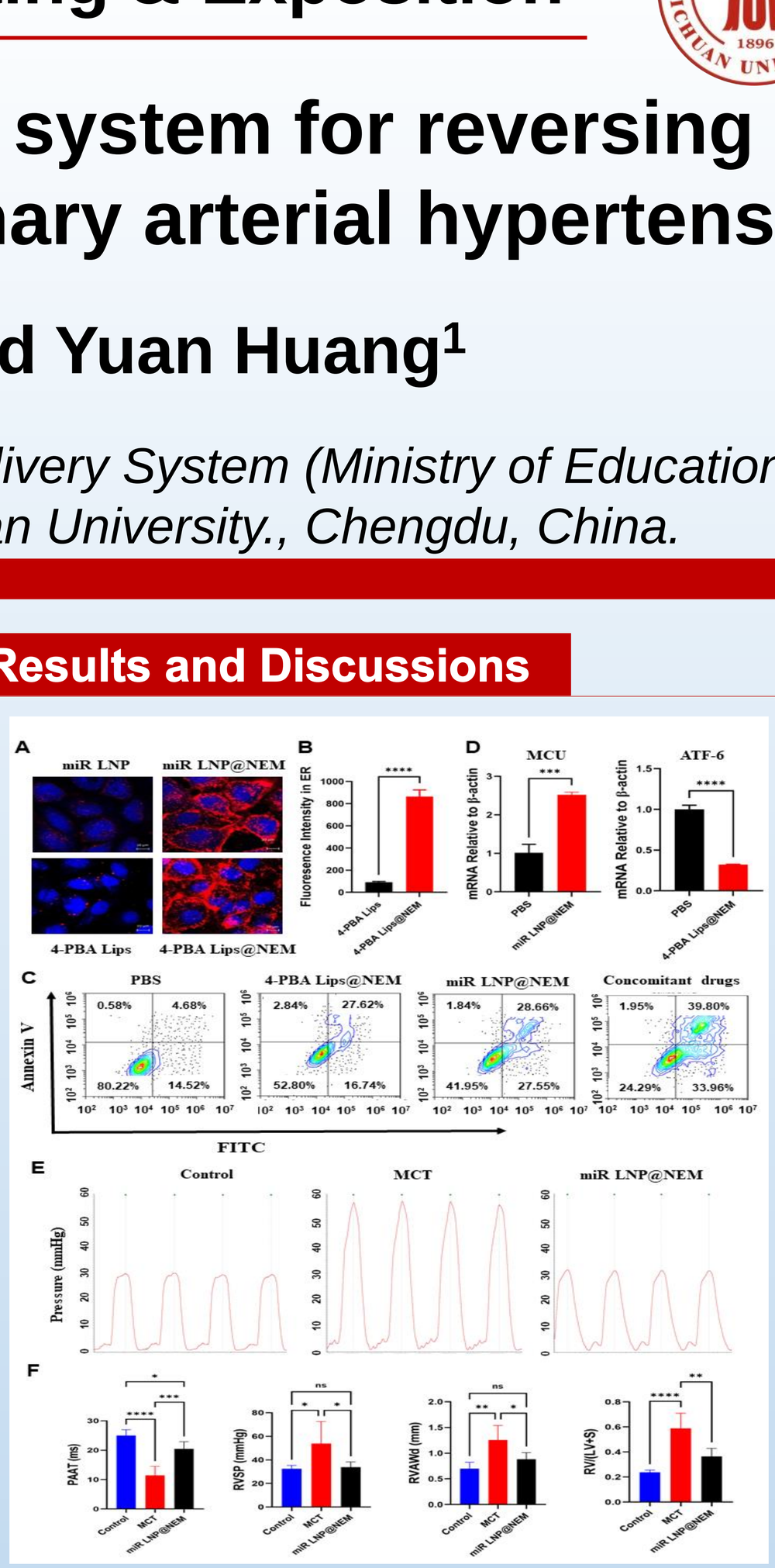

Fig.2 (A) In vitro targeting of BLDS to inflammatory HUVECs. (B) The mean fluorescence intensity of Lips@NEM in ER. (C) The cell apoptosis rate of PAH PASMC. (D) mRNA expression of MCU，ATF6 in PAH PASMC. (E) The RVSP in MCT-induced Sprague-Dawley rats. (F) The quantified hemodynamics PAAT , RVSP , RVAWd and Fulton's Index (RV/(LV+S)).

After being embedded with NEM, both 4-PBA Lips@NEM and miR LNP@NEM showed excellent inflammatory targeting ability in tumor necrosis factor-α(TNF-α) – activated HUVECs (Fig.2A). More interestingly, biomimetic liposomes could enhance ER retention capacity in PAH PASMCs compared with 4-PBA Lips (Fig.2B), where 4-PBA acts on the cells exactly. The co-delivery biomimetic system boosted the apoptotic rate of PAH PASMC by downregulating ATF6 and restoring MCU gene expression (Fig.2C-D.). In PAH , rats treated with miR LNP@NEM had notably lower right ventricular systolic pressure (RVSP) , right ventricular anterior wall diastolic (RVAWd) thickness and right ventricular hypertrophy, and improved pulmonary artery acceleration time (PAAT), compared with untreated group (Fig.2E-F)

4. Conclusions

The BLDS is successfully designed for the cascade - targeted inflammatory vascular cells and ER, has great potential to reverse vascular remodeling through specifically transporting therapeutic drugs to PAH tissues.

Reference

[1] Nature Reviews Disease Primers, 2024, 10(1): 1.
[2] Circulation, 2013, 127(1): 115-25.