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COMMENTARY

RDYH58 functionalized exosomes homing muscle fibroblasts for delivery of siRNA targeting FKBP10: A novel therapeutic strategy for idiopathic pulmonary fibrosis

KEY WORDS

Idiopathic pulmonary fibrosis;
Myofibroblasts;
FK506-binding protein;
RDYH58;
Exosomes;
Drug delivery

Idiopathic pulmonary fibrosis (IPF) is a progressive interstitial lung disease with a median survival of 3−5 years after diagnosis[1], exhibiting particularly high incidence and mortality rates in Europe and North America[2]. Its pathological mechanisms involve epithelial cell activation, recurrent lung tissue injury, and impaired repair, leading to fibroblast activation, excessive transforming growth factor β (TGF-β) secretion, and extracellular matrix (ECM) accumulation, thereby impairing alveolar gas exchange[3]. Myofibroblasts play a pivotal role in this process, secreting α-smooth muscle actin (α-SMA) to drive fibrosis progression[4]. Existing therapeutics such as pirfenidone and nintedanib only delay disease progression but carry risks of hepatotoxicity and gastrointestinal side effects. Therefore, developing novel therapeutic strategies targeting myofibroblasts is urgently needed.

FK506-binding protein (FKBP10) has been identified as a therapeutic target in IPF due to its role in collagen regulation. It is a procollagen chaperone protein that is upregulated in IPF and primarily localized to myofibroblasts. Downregulation of FKBP10 expression reduces collagen and fibronectin (FN) production and inhibits myofibroblast migration. However, no small-molecule inhibitors targeting FKBP10 are currently available. Fortunately, the FKBP10 transcription sequence can be used to design FKBP10-specific siRNA (siFKBP10). It is advisable to develop a delivery system carrying siFKBP10 as alternative therapeutics. For delivering siRNA, exosomes are highly ideal carriers. As small vesicles with diameters of 30−150 nm secreted by all cell types, they represent the smallest subtype of extracellular vesicles and are less susceptible to phagocytosis by macrophages and lysosomes. However, the physiological characteristics of the lung and the structural properties of siRNA make delivering siRNA therapeutics to specific lung cells challenging, and the efficiency of siRNA delivery to the lung still requires significant improvement.

Recently, Yuan et al.[5] published an innovative study in *Acta Pharmaceutica Sinica B*, designing RDYH58 peptide-functionalized exosomes (RDYH58-exo) to target myofibroblasts and load them with siFKBP10 (RDYH58-siFKBP10). This approach alleviated IPF by inhibiting collagen synthesis. The authors engineered the RDYH58 peptide fused with the exosomal membrane protein Lamp2b to construct targeted exosomes, which were efficiently loaded with siFKBP10 using ultrasonic microfluidics. *In vitro* and *in vivo* experiments demonstrated that RDYH58-siFKBP10 specifically targets myofibroblasts, significantly suppressing FKBP10 expression and ECM deposition, showcasing the potential of this novel therapeutic strategy.

They first transfected HEK293F cells with a plasmid expressing RDYH58-Lamp2b-HA. Expression of exosome markers was validated *via* Western blot (WB), and RDYH58-modified exosomes were isolated. Following drug loading *via* ultrasonic microfluidics, the loading efficiency of siFKBP10 reached 28%−35%, with exosome particle sizes maintained at 92.5−99.8 nm and a slight decrease in zeta potential.

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Transmission electron microscopy (TEM) and nanoparticle tracking analysis (NTA) revealed intact exosome morphology and stable loading structures.

In a bleomycin (BLM)-induced pulmonary fibrosis model, RDYH58-exo demonstrated high affinity for myofibroblasts, significantly enhancing cellular uptake efficiency. *In vivo* experiments delivered labeled exosomes to IPF model mice *via* tracheal nebulization. Small animal imaging revealed RDYH58-exo accumulation in the lungs, co-localizing with myofibroblasts and macrophages. Immunofluorescence staining and WB analysis further demonstrated that RDYH58-siFKBP10 significantly suppressed the expression of FKBP10, α-SMA, collagen type I (Col-1), and fibronectin (FN), while alleviating fibrotic symptoms.

In an IPF mouse model, nebulized administration of RDYH58-siFKBP10 significantly reduced lung weight, collagen area, and hydroxyproline content while improving alveolar structure. RNA-seq analysis revealed that post-treatment genes were involved in ECM−receptor interactions and the PI3K−Akt pathway, while angiogenesis-related genes were upregulated, indicating that this strategy exerts anti-fibrotic effects by downregulating fibrotic factors.

In addition, based on the current encouraging outcome, more efforts should be put into the ongoing study to promote clinical translation. Herein, we would like to provoke some discussion. The following discussion points are proposed: (1) Challenges in large-scale exosome production. Although the authors demonstrated the potential for exosome preparation in laboratory settings, large-scale production remains difficult. Ultracentrifugation yields are low and difficult to scale up, while the lack of standardized separation methods leads to high batch-to-batch heterogeneity. Future efforts should optimize bioreactor expansion processes, and establish standardized separation protocols to advance clinical applications. (2) Comparative studies with existing drugs in clinic. Direct comparative studies between RDYH58-siFKBP10 and established therapies (*e.g.*, pirfenidone, nintedanib) are recommended to quantitatively evaluate its therapeutic advantages. (3) Regulatory pathway challenges for exosome-siRNA combination therapies. Although the RDYH58-exo/siFKBP10 system developed in this study demonstrated significant therapeutic potential in preclinical research, such exosome−siRNA conjugate products face unique regulatory pathway challenges during clinical translation. Future progress urgently requires synergistic advancement in regulatory science, enhanced early communication between regulatory agencies and developers, and exploration of flexible risk-based regulatory strategies. This aims to establish clear, predictable regulatory pathways for such innovative combination therapies, accelerating their journey to benefit patients.

In summary, Yuan et al.'s research provided an innovative targeted delivery platform for IPF treatment. By combining peptide targeting with an exosome carrier, it achieved precise delivery of siFKBP10 and effectively slows the progression of fibrosis. This strategy not only demonstrated efficacy in IPF management but also held potential for extension to other fibrotic diseases, showcasing broad clinical prospects.

Author contributions

Mengqin Guo, analysis and manuscript writing; Wenhao Wang, writing-review & editing; Chuanbin Wu, supervision and proofreading; Zhengwei Huang, writing-review & editing, conceptualization.

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