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COMMENTARY

Unlocking the therapeutic potential of RNA splicing in lung fibrosis: Insights from the SRSF7−PKM axis

KEY WORDS

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PKM exon skipping;
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Lomitapide

Breathing, an essential physiological process, enables the continuous exchange of gases necessary for maintaining internal metabolic balance. On average, an adult inhales and exhales roughly 10,000 to 12,000 L of air each day to sustain adequate oxygen levels[1]. The lungs, which serve as the body's primary organs for gas exchange, possess a remarkable intrinsic capacity for self-repair and regeneration following injury[2,3]. When this repair mechanism becomes dysregulated, it may lead to progressive and irreversible lung diseases[4,5]. Among these, lung fibrosis stands out as a particularly devastating and irreversible interstitial lung disease, characterized by relentless accumulation of scar tissue, architectural distortion, declining lung function, and ultimately respiratory failure. Idiopathic pulmonary fibrosis (IPF), the most common subtype, has a median survival of only 3−5 years following diagnosis, with a 5-year mortality rate exceeding 50%[6]. Although anti-fibrotic medications including pirfenidone and nintedanib are currently in clinical use and offer moderate benefits in slowing disease progression, they do not halt or reverse lung fibrosis. Lung transplantation remains the only potentially curative treatment but is severely limited by donor availability, immunologic complications, and high financial burden. These challenges underscore the urgent need to elucidate the molecular and cellular mechanisms underlying lung fibrosis and to develop effective therapeutic strategies.

Persistent fibroblast activation and differentiation into myofibroblasts, leading to aberrant extracellular matrix (ECM) deposition, is a hallmark of fibrotic lung pathology[7]. Alternative splicing, a post-transcriptional process that allows a single gene to encode multiple transcript variants, plays a pivotal role in regulating cellular metabolism, proliferation, differentiation, and programmed cell death[8]. By expanding transcriptomic and proteomic diversity, alternative splicing is increasingly recognized as a modulator of fibroblast phenotype and metabolic plasticity. However, direct evidence linking specific splicing regulators to fibrotic disease processes has remained relatively sparse.

In a recent study published in *Acta Pharmaceutica Sinica B*, Jin et al.[9] provide compelling data suggesting that serine/arginine-rich splicing factor 7 (SRSF7) promotes fibroblast proliferation and activation in lung fibrosis by regulating alternative splicing of pyruvate kinase M (PKM) to enhance glycolytic flux. This work identifies a previously unrecognized splicing−metabolism axis as a key driver of fibroblast reprogramming in lung fibrosis.

The authors observed elevated SRSF7 protein levels in fibrotic lung tissue from both human patients and mice subjected to bleomycin-induced lung injury. Single-cell transcriptomics further pinpointed SRSF7 expression within fibroblast clusters marked by high expression of fibrogenic genes such as COL1A1, FN1, and ACTA2. Functional studies revealed that overexpression of SRSF7 aggravates lung fibrosis *in vivo*, and promotes activation, proliferation, and ECM production in primary lung fibroblasts *in vitro*. These observations support the role of SRSF7 as an important regulator of fibroblast plasticity and underscore its pathological significance in fibrogenesis.

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Mechanistically, the authors showed that SRSF7 directly binds to the PKM transcript and facilitates exclusion of exon 2 (E2), resulting in the generation of a previously uncharacterized isoform, PKMΔE2. This splice variant was associated with enhanced glycolysis, increased lactate production, and a profibrotic fibroblast phenotype. Importantly, forced expression of PKMΔE2 recapitulated the pro-fibrotic effects of SRSF7, whereas knockdown of PKMΔE2 reduced fibroblast activation, indicating that this splicing event is not only necessary but also sufficient to drive fibrotic changes. These findings further reinforce the notion that metabolic rewiring toward glycolysis is a defining feature of activated fibroblasts and highlight the functional consequences of splicing-mediated metabolic regulation in fibrotic disease.

Extending these insights to therapeutic exploration, the authors conducted a high-throughput drug screen and identified lomitapide, a cholesterol-lowering agent approved for homozygous familial hypercholesterolemia[10], as a potential SRSF7 inhibitor. Lomitapide reduced SRSF7 expression, diminished PKM exon 2 skipping, and markedly alleviated lung fibrosis in bleomycin-treated mice. These results suggest that pharmacologic inhibition of SRSF7 may hold promise as a novel strategy for treating lung fibrosis and exemplify how mechanism-driven drug repurposing can uncover viable treatment avenues for complex fibrotic diseases.

This study opens exciting avenues for future research. One pressing question is what drives the upregulation of SRSF7 within fibrotic niches—whether epigenetic remodeling, inflammatory signaling, or mechanical stress is responsible, remains to be elucidated. Beyond its role in alternative splicing, SRSF7 may also participate in mRNA export or translational regulation, broadening its functional repertoire in lung fibrosis. It also remains unclear whether the PKMΔE2 isoform is functionally distinct from classical PKM beyond glycolysis, potentially impacting redox homeostasis or transcriptional dynamics. Targeting this splicing−metabolism axis presents therapeutic promise, and combinatorial approaches co-inhibiting splicing regulators and metabolic pathways may yield synergistic anti-fibrotic effects. Structural biology approaches such as AlphaFold3-based modeling and cryo-electron microscopy (cryo-EM) could provide detailed insights into the SRSF7−PKM RNA complex and the structural basis for PKMΔE2's altered enzymatic activity. Similarly, elucidating the precise mechanism by which lomitapide inhibits SRSF7 *via* structural studies of drug−protein complexes may guide the rational AI-assisted design of next-generation SRSF7-targeting small molecules with enhanced specificity and pharmacological potential.

In conclusion, the work by Jin et al. illuminates a mechanistic link between RNA splicing and metabolic reprogramming in lung fibrosis. By identifying SRSF7 as a modulator of fibroblast metabolism through alternative splicing of PKM, the study provides new insight into fibrotic disease pathogenesis and highlights a potential therapeutic target. Their findings not only enhance our understanding of fibrotic biology but also pave the way for the development of splicing-targeted therapies in lung fibrosis.

References

1. Neupane AS, Willson M, Chojnacki AK, Vargas E, Silva Castanheira F, Morehouse C, et al. Patrolling alveolar macrophages conceal bacteria from the immune system to maintain homeostasis. *Cell* 2020;**183**:110−25.e11.
2. Jones DL, Morley MP, Li X, Ying Y, Zhao G, Schaefer SE, et al. An injury-induced mesenchymal−epithelial cell niche coordinates regenerative responses in the lung. *Science* 2024;**386**:eado5561.
3. Liu K, Meng X, Liu Z, Tang M, Lv Z, Huang X, et al. Tracing the origin of alveolar stem cells in lung repair and regeneration. *Cell* 2024;**187**:2428−45.e20.
4. Mo C, Li H, Yan M, Xu S, Wu J, Li J, et al. Dopaminylation of endothelial TPI1 suppresses ferroptotic angiocrine signals to promote lung regeneration over fibrosis. *Cell Metab* 2024;**36**:1839−57.e12.
5. Ma J, Zhang L, Zhang X, Zhang L, Zhang H, Zhu Y, et al. Inhibiting endothelial *Rhoj* blocks profibrotic vascular intussusception and angiocrine factors to sustain lung regeneration. *Sci Transl Med* 2024;**16**:eado5266.
6. Chen Y, Li Z, Ji G, Wang S, Mo C, Ding BS. Lung regeneration: diverse cell types and the therapeutic potential. *MedComm* 2024;**5**:e494.
7. Fang Y, Chung SSW, Xu L, Xue C, Liu X, Jiang D, et al. RUNX2 promotes fibrosis *via* an alveolar-to-pathological fibroblast transition. *Nature* 2025;**640**:221−30.
8. Marasco LE, Kornblihtt AR. The physiology of alternative splicing. *Nat Rev Mol Cell Biol* 2023;**24**:242−54.
9. Jin T, Gao H, Wang Y, Ning Z, Bing D, Wang Y, et al. SRSF7 promotes pulmonary fibrosis through regulating PKM alternative splicing in lung fibroblasts. *Acta Pharm Sin B* 2025;**15**:3041−58.
10. Brunham LR, Hegele RA. Lomitapide for the treatment of homozygous familial hypercholesterolaemia in children. *Lancet Diabetes Endocrinol* 2024;**12**:866−7.

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