Towards causal validation and clinical translation of the PAK2–fibroblast axis in idiopathic pulmonary fibrosis

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To the Editor:

We read with great interest the article by Watanabe *et al.* [1], which integrates spatial and single-cell transcriptomics to identify a WNT5A^{+}CTHRC1^{+} myofibroblast subset and implicates p21-activated kinase 2 (PAK2) activation as a potential therapeutic driver in idiopathic pulmonary fibrosis (IPF). As spatial multi-omics technologies reshape our understanding of fibrotic microenvironments, defining cell-specific causal pathways and clinically actionable targets has become a central challenge in translational respiratory research. While we commend the authors for identifying a spatially restricted fibroblast population with therapeutic relevance, we believe several mechanistic and translational questions remain before PAK2 can be established as a validated, disease-defining target.

First, regarding mechanistic causality and cell specificity, the current study stops short of establishing a causal and fibroblast-restricted role of PAK2 within the fibrotic niche. Although pharmacological inhibition attenuates fibrosis in the bleomycin model, the observed effect remains correlative. The spatial co-localisation of PAK2 with WNT5A^{+}CTHRC1^{+} fibroblasts may reflect convergent features of terminal remodelling rather than a directional pathogenic link [2]. Moreover, FRAX-series inhibitors target multiple PAK isoforms across epithelial, immune and stromal compartments, making systemic modulation a likely contributor to the therapeutic response. To delineate causality, fibroblast-specific perturbation models – such as *Pdgfrα-Cre; Pak2$^{fl/fl}$* – or temporally resolved CRISPR (clustered regularly interspaced short palindromic repeats) interference, should be paired with spatial and single-cell profiling to determine whether selective PAK2 suppression alters fibroblast behaviour and fibrotic architecture [3]. Emerging spatial perturbation tools such as Slide-seq or GeoMx DSP may help map the temporal dynamics of PAK2 signalling under selective inhibition. Establishing such cell-intrinsic causality is pivotal to validating PAK2 as a *bona fide* therapeutic target rather than a passive biomarker.

Second, at the immune–epithelial interface, the upstream signalling events leading to PAK2 activation remain undefined, limiting the mechanistic completeness of the fibroblast-centric framework. IPF is increasingly recognised as a multicellular disorder shaped by epithelial injury, immune-derived cytokines, and dysregulated repair loops [4]. The observed immune infiltration adjacent to fibroblastic foci in the study suggests that PAK2 upregulation may reflect microenvironmental reprogramming rather than an autonomous fibroblast-intrinsic programme [5]. To fully contextualise PAK2 activation within this multicellular landscape, deciphering intercellular communication requires spatial interactomics approaches, including ligand–receptor inference and multiplex imaging, to track signalling exchanges between immune, epithelial and stromal elements. In addition, phosphoproteomic profiling following PAK inhibition could reveal immune–stromal feedback rewiring that may undercut treatment durability or drive resistance. Determining whether PAK2 functions as a context-dependent responder or an upstream effector will critically inform its utility as a therapeutic target.

Third, from a translational standpoint, the therapeutic trajectory for PAK2 inhibition remains underdeveloped, encompassing questions of patient stratification, therapeutic window and drug-delivery feasibility. By analysing only end-stage explants, the study offers limited insight into whether PAK2 activation occurs during earlier or progressive phases of disease when intervention may still be effective. Without longitudinal or antifibrotic-exposed spatial datasets, the timing of therapeutic vulnerability remains

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While PAK2 marks fibrotic fibroblast niches in IPF, causal validation, multicellular contextualisation and lung-targeted delivery are required before clinical translation. Spatial omics should guide not only discovery but also therapeutic decision-making. https://bit.ly/4hqQS3F

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speculative [6]. Furthermore, inter-individual variability was not addressed; identifying a "PAK2-high" molecular subtype associated with clinical endpoints such as forced vital capacity decline, survival, or antifibrotic response could greatly enhance clinical utility. Systemic administration of FRAX compounds also raises safety concerns, given PAK2 expression in the myocardium, central nervous system and immune tissues [7]. Lung-targeted delivery platforms, including inhaled nanoformulations or AAV (adeno-associated virus)-based vectors, should be explored to maximise on-target efficacy while minimising off-target toxicity. Future studies may also consider developing PAK2-based predictive models that integrate molecular subtype stratification with imaging and lung function parameters, facilitating early therapeutic decision-making.

In summary, while this study offers a compelling spatial map of fibroblastic foci and dense fibrosis, translating spatial-omics discoveries into viable therapies requires more than target nomination: it demands causal validation, immune ecosystem contextualisation, and precision medicine strategies. As respiratory medicine moves into the era of spatially guided intervention, integrating single-cell analytics with real-world clinical phenotyping will be crucial to define who benefits, when to intervene, and how to deliver treatment safely. While the study by Watanabe *et al*. [1] provides an important spatial blueprint of the fibrotic niche, we believe the next step lies in multi-scale integration: linking spatial pathology to mechanistic causality, therapeutic feasibility, and responsible clinical translation. We hope this work catalyses such efforts within the respiratory research community.

Man Sun[1,2], Dan Zang[1,2] and Jun Chen[1]

[1]Department of Oncology, The Second Hospital of Dalian Medical University, Dalian City, China. [2]These authors contributed equally to this work.

Corresponding author: Jun Chen (chenjun_dmu@126.com)

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