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INTERVIEW

The people behind the papers – Yongjun Yin and David Ornitz

During alveologenesis, multiple mesenchymal cell types play crucial roles in maximising the lung surface area. In their study, David Ornitz and colleagues define the repertoire of lung fibroblasts, with a particular focus on alveolar myofibroblasts. To know more about their work, we spoke to the first author, Yongjun Yin, and the corresponding author, David Ornitz, Alumni Endowed Professor at the Department of Developmental Biology, Washington University School of Medicine, St. Louis.

Yongjun Yin (left) and David Ornitz (right)

David, can you give us your scientific biography and the questions your lab is trying to answer?

DO: I received my BS degree from the University of California, Davis in 1981 and my MD and PhD from the University of Washington, Seattle, in 1987. As a graduate student, I was at the forefront of developing transgenic mouse technology for *in vivo* models of cancer and as tools to identify tissue-specific transcriptional regulatory elements. During my postdoctoral training at Harvard Medical School, I developed a binary genetic system to model cancer and other lethal diseases in mice and discovered that heparan sulphate proteoglycans are necessary co-factors for fibroblast growth factor (FGF) signalling. I joined the faculty at Washington University in St. Louis School of Medicine in 1991 and over the past 33 years, my research has focused on the *in vivo* function of FGFs in development, physiology, response to injury, and cancer. My interest in lung development initiated with the discovery that fibroblast growth factor 9 (*Fgf9*) has a unique expression pattern in developing lung epithelium and mesothelium. By engineering a mouse in which the *Fgf9* gene is inactivated, we discovered that FGF9 has a major role in the regulation of lung branching morphogenesis. My current focus in lung biology has shifted to alveologenesis, the final stage of lung development. *Fgf18* expression is induced during alveologenesis. To study its function during alveologenesis, we again engineered genetic tools that target the *Fgf18* gene, allowing us to study unique cell populations that contribute to alveologenesis and probe the function of FGF18 during this process. Additional information about my research group can be found on our website: http://ornitzlab.wustl.edu/.

Yongjun, how did you come to work in the lab and what drives your research today?

YY: Initially, I trained as a physician in China. When I finished my medical training, I felt that there were many things that you could not to do to improve the treatment of patients. To explore research opportunities, I entered a three-year Master's programme. This really allowed me to try a lot of things that I could not do directly with patients. I fell in love with lab research and decided to pursue a PhD in oncology, with a focus on breast and prostate cancer, from the Hebrew University. I joined Dr Ornitz's lab as a postdoctoral fellow to study the role of FGF signalling in lung development and cancer. Currently, my focus is on alveologenesis in the mouse lung using our unique $Fgf18^{CreER}$ tool. I am particularly interested in the fate of the myofibroblast during postnatal alveologenesis. I believe that our studies will contribute to the understanding of mesenchymal cell dynamics and provide insight into the prevention or treatment of bronchopulmonary dysplasia in premature infants and lung fibrosis in adults.

Tell us about the background of the field that inspired your work

YY & DO: Alveologenesis is one of the most clinically relevant stages of lung development when the gas exchange surface area of the lung is increased by the formation of secondary septae in alveolar saccules, followed by thinning of the septal walls. Impaired alveologenesis is a major cause of morbidity in extremely preterm infants and often results in bronchopulmonary dysplasia. Multiple cell types, including epithelial, mesenchymal and endothelial cells, must interact to form secondary septae. The identity of the mesenchymal cell types and their lineage relationships during alveologenesis is poorly understood, which is the focus of this paper.

Can you give us the key results of the paper in a paragraph?

YY & DO: With a unique $Fgf18^{CreER}$ mouse line for lineage tracing, we used cell sorting, single-cell RNA sequencing, and primary cell culture to identify multiple subtypes of mesenchymal cells in the neonatal lung. These mesenchymal cell types include an immature progenitor cell that gives rise to mature myofibroblasts,

Department of Developmental Biology, Washington University School of Medicine, St. Louis, MO63110, USA.
E-mail: dornitz@wustl.edu

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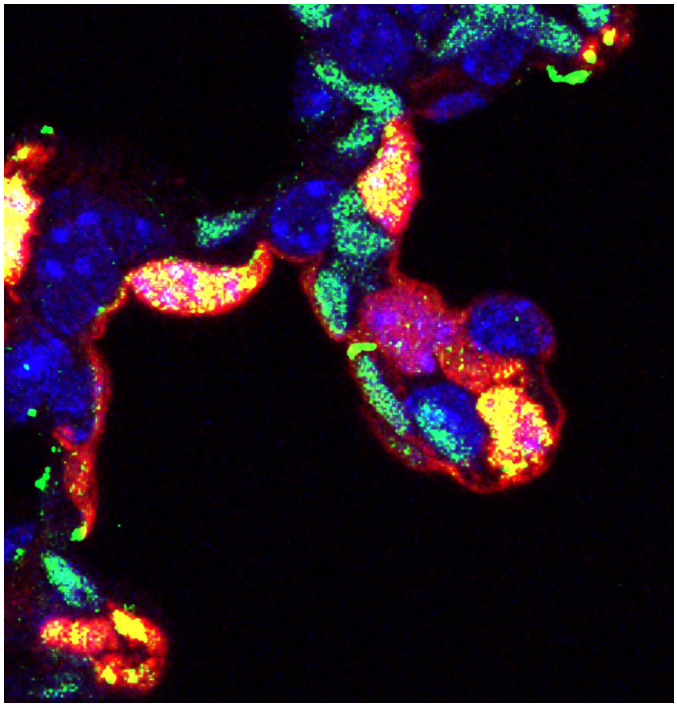

A secondary septum in a developing alveolus. FGF18 lineage trace (red) marks myofibroblasts and alveolar type 1 cells. Mature myofibroblasts (yellow) co-express the FGF18 lineage trace and Connexin 43 (green). Nuclei are stained by DAPI (blue). Credit: Yongjun Yin.

and several types of matrix and adventitial fibroblasts. We also found that the endogenous and targeted *ROSA26* locus serves as a sensitive reporter for myofibroblast maturation. In culture, myofibroblast progenitors mature, whereas matrix fibroblasts appear stable. These studies identify a myofibroblast differentiation programme that is distinct from other mesenchymal cell types and increases the known repertoire of mesenchymal cell types in the neonatal lung.

Yongjun, when doing the research, did you have any particular result or eureka moment that has stuck with you?

YY: The realisation that a combination of the *Fgf18*^{CreER} lineage tracing and *Pdgfra*^{EGFP} could be used to sort functionally distinct mesenchymal cell types made these studies possible and allowed the myofibroblasts to be separated into immature and mature subpopulations. We were also a bit lucky in finding that the *ROSA26* locus itself can serve as a marker for myofibroblast maturation. One big eureka moment was when we figured out the culture conditions for sorted lung mesenchymal cells. Although these eureka moments do not last that long, they are the driving force motivating us to pursue new ideas and understand mechanisms.

Yongjun, and what about the flipside: any moments of frustration or despair?

YY: Yes, I must say, there were many moments of frustration and despair. For instance, our cell cultures experienced an unexpected halt in their growth, resulting in cell death. Despite of our efforts to improve the situation, this persisted for about 3 months.

Why did you choose to submit this paper to Development?

YY & DO: We felt that Development is a well-respected journal that would give good visibility to our work. We were also very pleased with the efficiency and quality of the review process.

Yongjun, what is next for you after this paper?

YY: In this paper, we showed data from wild-type mice. For our next goal, we want to understand how FGF18 regulates the process of alveologenesis. We are particularly interested in the cell types that receive the FGF18 signal and the nature of their response to FGF18. We hope that we will find a role for FGF18 in alveologenesis and its relationship with the postnatal fate of the myofibroblast. We are starting to get a lot of interesting data and are very excited about this project.

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David, where will this story take your lab next?

DO: The single-cell RNA-sequencing data allowed us to generate multiple hypotheses about target cells, novel transcription factors that regulate these cells, and potential mechanisms that regulate the specificity of FGF18 signalling. We are very excited to pursue these and other directions to improve our understanding of the molecular and cellular mechanisms that regulate alveologenesis.

Finally, let's move outside the lab – what do you like to do in your spare time?

DO: My spare time includes running, biking and hiking. I relax by cooking, gardening and watching science fiction.

YY: At home, I love cooking and baking. I also like to watch TV programmes about forensic science helping to solve crimes.

Reference

Yin, Y., Koenitzer, J. R., Patra, D., Dietmann, S., Bayguinov, P., Hagan, A. S. and Ornitz, D. M. (2024). Identification of a myofibroblast differentiation program during neonatal lung development. *Development* **151**, dev202659. doi:10.1242/dev.202659