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FIRST PERSON

First person – Zhang Li

First Person is a series of interviews with the first authors of a selection of papers published in Disease Models & Mechanisms, helping researchers promote themselves alongside their papers. Zhang Li is first author on 'A kidney resident macrophage subset is a candidate biomarker for renal cystic disease in preclinical models', published in DMM. Zhang is a postdoc in the lab of Bradley Yoder at University of Alabama at Birmingham, Birmingham, AL, USA, investigating the roles of renal macrophages and kidney injury in the pathology of cystic kidney diseases.

How would you explain the main findings of your paper to non-scientific family and friends?

Autosomal-dominant polycystic kidney disease (ADPKD) is one of the most common inherited genetic renal disorders and affects more than 13 million people worldwide. It is a progressive and, unfortunately, incurable disorder that leads to significant morbidity and kidney failure. The severity of polycystic kidney disease (PKD) is highly variable among patients, and it is difficult to measure and predict disease. This emphasizes the need to identify potential easy-to-measure biomarkers for an effective patient diagnosis and for future testing of possible therapies. Our approach was to investigate the accumulation of macrophages in cystic kidney and utilize both preclinical mouse PKD models and kidney tissues along with urine samples from ADPKD patients. We identified a subset of macrophages that accumulate around the renal cysts, and, more importantly, the number of macrophages in patient urine samples correlates well with the rate of disease progression in these patients. We propose that this subpopulation of macrophages could serve as a biomarker for tracking disease progression in PKD patients.

What are the potential implications of these results for your field of research?

One of the key findings of our study was identifying a subset of renal macrophages associated with cysts in both animal and patient kidneys. Our single-cell RNA-sequencing analysis indicated that this population is conserved in both mouse and human kidney. These data support translational studies on the role of macrophages in the pathology of PKD. In addition, our study suggested that the macrophage subset detectable in urine samples could serve as a biomarker for disease progression. This type of analysis could benefit PKD patients, given that the urinary test is a convenient and non-invasive way to predict disease progression compared to the current standard measurement of total kidney volume that is determined through ultrasound or magnetic resonance imaging. The presence of these cells may also help in clinical trials to evaluate efficacy of potential drugs to slow disease progression.

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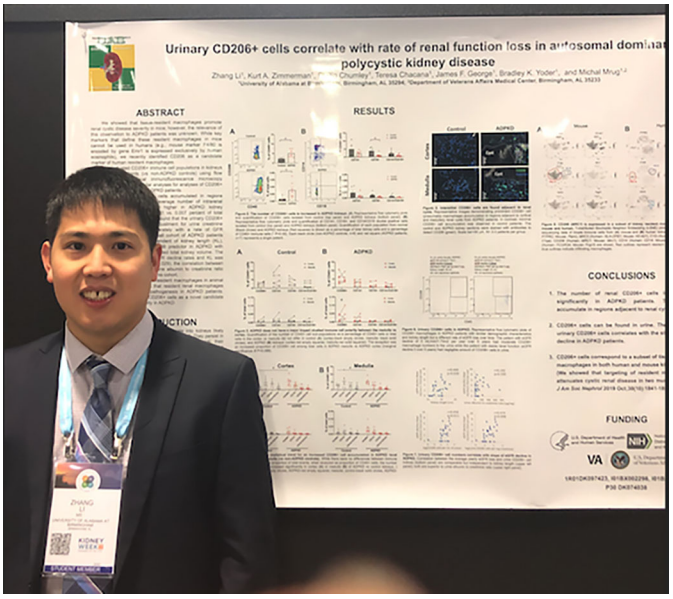

Zhang Li

What are the main advantages and drawbacks of the experimental system you have used as it relates to the disease you are investigating?

Our studies utilized a conditional knockout (cKO) PKD mouse model. The major advantage of this model is that we can manipulate the time of *Pkd2* gene deletion with tamoxifen induction. This approach avoids the embryonic lethality that happens in congenic knockout models. Furthermore, this inducible cKO model provides more controlled conditions where the rates of cyst progression are more predictable than in human patients, enabling us to more easily investigate the mechanism of cyst progression. The major drawback comes from the fact that patients' disease progression occurs slowly over decades, and most cysts originate from the collecting ducts, whereas in the mouse models the timing and location is different. These differences could potentially lead to the discrepancies between the preclinical data and the clinical trials, but that is a common concern in PKD research. With that being said, we benefit from having access to both animal models and PKD patient tissue samples for our experiments. The drawbacks of working on human samples, however, are obvious. It always takes more time and effort to acquire these patient samples.

"The results of this paper highlight that macrophages may have a more direct role in driving cyst formation."

What has surprised you the most while conducting your research?

Previous studies from our lab have demonstrated the role of macrophages in cyst formation after ischemia/reperfusion injury in the cystic kidney model. Given that macrophages play a major role in mediating injury response in the kidney, it is possible that the reduction

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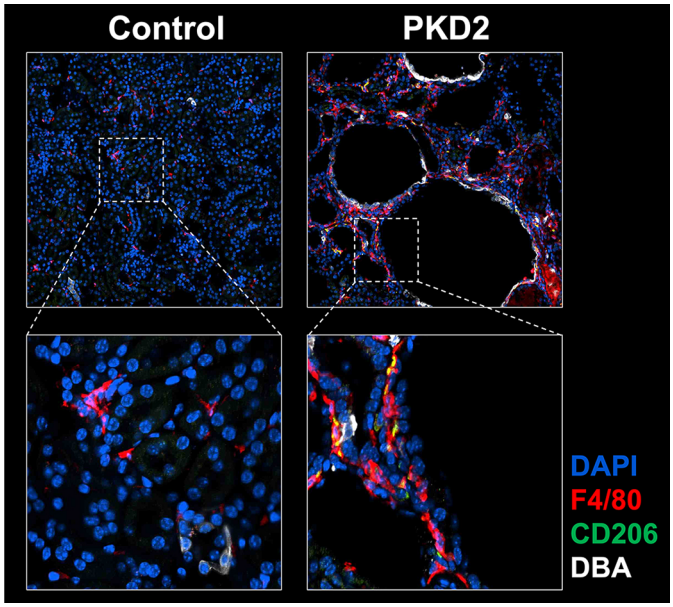

Immunofluorescence staining of kidneys from control and *Pkd2* mutant mice at 16 weeks post tamoxifen induction. More CD206$^+$ macrophages accumulate around cysts in *Pkd2* mutant kidney than in control kidney.

in cyst severity with macrophage depletion is simply a result of a reduced level of the injury rather than a direct effect of macrophages on cyst expansion. Therefore, we were concerned that the deletion of macrophages with CX3CR1 mutation in this study may not affect cystic phenotypes in PKD mutant mice without any exogenous injury. But that turned out to not be the case. Therefore, the results of this paper highlight that macrophages may have a more direct role in driving cyst formation. Our long-term goal is to understand the mechanisms involved in cyst formation along with the development of potential avenues for the attenuation of this pathology.

What do you think is the most significant challenge impacting your research at this time and how will this be addressed over the next 10 years?

PKD remains incurable. Although there are many studies investigating every aspect of this disease, the preclinical or clinical studies do not always appear encouraging. I believe making our research findings translatable to human disease is the most important challenge in the field. Although we have developed many useful animal model systems, to completely ensure that our research findings are robust and translatable, complementary studies have to be performed on human tissue. To overcome this challenge, I believe an integrated collaboration between basic scientists, patients and clinicians is the best approach. There are many research samples, and databases could be utilized and, importantly, shared between researchers and clinicians. My hope is that, in the near future, more comprehensive and publicly available databases of patient samples can be established for the research community.

“A supportive mentor is extremely important for people choosing research as their career.”

What changes do you think could improve the professional lives of scientists?

Personally, as an early-career scientist, I think having more funding opportunities and fellowships, particularly those that help with the transition from postdoctoral trainee to a fully independent academic research scientist, are important for improving the professional lives of scientists. In addition, I firmly believe a supportive mentor is extremely important for people choosing research as their career. The mentor should not only focus on research or experiments with trainees, but should also provide resources and opportunities for training for their career development as early as college and graduate school. With good guidance and encouragement from mentor, the mentee will have more enthusiasm to pursue an academic career with creativity and production.

What’s next for you?

I just started my postdoctoral fellowship, and am looking forward to furthering this study by examining the function of this CD206$^+$ resident macrophages subset and the underlying molecular signalling driving cyst progression by generating a mouse model that specifically depletes CD206$^+$ resident macrophages. In the long term, I would like to choose an academic path in my career, and I look forward to continuing my research in kidney injury and cystic kidney disease, and eventually directing my own lab.

Reference

Li, Z., Zimmerman, K. A., Cherakara, S., Chumley, P. H., Collawn, J. F., Wang, J., Haycraft, C. J., Song, C. J., Chacana, T., Andersen, R. S. et al. (2023). A kidney resident macrophage subset is a candidate biomarker for renal cystic disease in preclinical models. *Dis. Model. Mech.* **16**, dmm049810. doi:10.1242/dmm.049810