THE OHIO STATE UNIVERSITY
BIOMEDICAL SCIENCES
GRADUATE PROGRAM
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Ashley R. Jackson
PhD Candidate

“Significance of Renal Urothelium During Development and Disease”

March 31, 2016
Graves 1167
1:00pm
VITA

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2007 . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . Biology
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ABSTRACT

Congenital obstructive nephropathy is the most common cause of chronic kidney disease in children and represents a tremendous societal burden in terms of morbidity and mortality. Despite surgical intervention, more than half of the children with congenital obstructive nephropathy progress to end stage renal disease mandating the development an appropriate mouse model to directly assess pathogenesis. Our lab uses the megabladder (mgb) mouse, which develops overt urinary tract obstruction in utero. Mgb⁻/⁻ mice exhibit hydronephrosis and progressive renal failure after birth providing an ideal model for the identification of molecular pathways involved in the pathogenesis of congenital obstructive nephropathy. I hypothesize that congenital obstructive nephropathy in the mgb⁻/⁻ mouse triggers an adaptive response in the kidneys, which is mediated by early changes in the renal urothelium.

We evaluated global renal transcriptomes in mgb mice through various stages of disease progression. Transcriptome analysis revealed an urothelial gene signature associated with worsening hydronephrosis. Although little is known about renal urothelium, its alterations during congenital obstructive nephropathy represent some of the earliest identified pathogenic events. Among the alterations, we identified a significant increase in urothelial proliferation that correlated with expansion of Krt14⁺ progenitor cells. We found that the normally single cell layered renal urothelium adapted to the obstruction by becoming multilayered. Schematically reconstructed proliferative regions revealed that some of the most dynamic were those juxtaposed to large neurovascular bundles. Furthermore, we identified expanded and de novo expression of hallmark urothelial specialization markers, including a family of proteins with a largely unknown function in the kidney, uroplakins.
Very little is known about the renal urothelium. Expression of uroplakins in the renal urothelium is controversial, and we have limited understanding of their function. Therefore, we evaluated Upk1b ablation using the Upk1b<sup>RFP/RFP</sup> mouse. We found that Upk1b is critical in urothelial plaque formation <i>in vivo</i>, as its absence caused aberrant expression of all other uroplakin family members consequently destabilizing the urothelial plaque. Upk1b<sup>RFP/RFP</sup> mice displayed dysplastic and dysfunctional bladder urothelium, and structurally deficient renal urothelium. We found that Upk1b is also critical in urothelial differentiation and progenitor regulation. Interestingly, a subset of Upk1b<sup>RFP/RFP</sup> mice displayed renal collecting system duplication, providing for the first time experimental evidence that Upk1b is involved in metanephric development.

While Upk1b was the highest expressed urothelial transcript and displayed graded increases to worsening hydronephrosis in the mgb<sup>-/-</sup> mouse, we still did not know if this was a beneficial adaptation. To test this, we ablated Upk1b in mgb<sup>-/-</sup> mice and during unilateral ureteral obstruction. In both models, absent Upk1b led to a worse outcome. The relevance of our studies has been born out by our evaluation of urothelial alterations during human congenital obstructive nephropathy. Preliminary data suggests children with ureteropelvic junction obstruction display urothelial alterations including increased proliferation and progenitor marker expression, mirroring those identified in our mouse studies.

Our work indicates that the renal urothelium is capable of adapting to lower urinary tract obstruction through modifying key structural proteins. Proper urothelial differentiation is critical for normal development and function as well as pathogenesis. Upk1b appears to play a key role in each of these processes. In summary, we implicate the renal urothelium in an early and important role during renal adaptation to congenital obstructive nephropathy. Exploiting these alterations may lead to the identification of diagnostic markers or even therapeutic avenues where permanent damage and end stage renal disease can be avoided.


SELECTED PUBLICATIONS (FROM 17)
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AWARDS AND HONORS

Invited to present published manuscript “Uroplakin 1b is critical in urinary tract development and urothelial differentiation and homeostasis” at the Pediatric Academic Society/American Society for Pediatric Nephrology Annual Meeting Baltimore, MD (May 2, 2016)

Recipient, Enrichment Award, Research Institute at Nationwide Children’s Hospital, 2015

Recipient, Travel Grant, American Society of Nephrology, Advances in Research Conference—Engineering Genomes to Model Disease, Target Mutations, and Personalize Therapy, 2015

Recipient, Travel Grant, 13th International Workshop on Developmental Nephrology, 2015

Recipient, Travel Grant, American Society of Nephrology, Advances in Research Conference—Building a Kidney: From Stem Cells to Function, 2014

Recipient, Academic Enrichment Award, Research Institute at Nationwide Children’s Hospital, 2014

FUTURE PLANS

I will be conducting my postdoctoral research in Dr. Brian Becknell’s lab at Nationwide Children’s Hospital. My goal is to identify context-specific roles for individual renal urothelial cell types during urinary tract development and injury. I am also interested in understanding the signaling mechanisms responsible for their regulation. Concomitantly, I will be applying for an F32 grant and continuing my education in Human Anatomy and Embryology to better position myself to for attaining my long-term career goal of becoming an NIH-funded principal investigator.