

THE GRADUATE COLLEGE OF THE  
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

## Vasileios Gerakopoulos

FOR THE DEFENSE OF THE DOCTOR OF PHILOSOPHY DEGREE  
GRADUATE COLLEGE

*Department of Cell Biology*

Meeting ID: 982 5298 4161

<https://ouhsc.zoom.us/j/98252984161?pwd=aTZib1RjNnh3ZHc5MlhGZHIUK1BZUT09>

Password: 03016722



Wednesday, July 15, 2020, 10:00 am

### *Role of the Polycystin complex in cell deciliation*

COMMITTEE IN CHARGE: Leonidas Tsiokas, PhD, Myron Hinsdale, PhD, Guangpu Li, PhD, Scott M. Plafker, PhD, RPh, Lawrence I. Rothblum, PhD

ABSTRACT: The primary cilium is an antenna-like organelle protruding from the surface of all cells, housing several signaling pathways. It follows a cyclic pattern of assembly and deciliation (disassembly and/or shedding), as cells exit and re-enter the cell

cycle, respectively. Autosomal dominant polycystic kidney disease (ADPKD) is caused by mutations in *Pkd1* and *Pkd2*, encoding a receptor-channel complex (Polycystins or PKD1/PKD2), present in the primary cilium. ADPKD is characterized by large fluid filled kidney cysts gradually leading to kidney failure. In mouse models of ADPKD, cilia ablation or acceleration of deciliation suppresses cystic growth, whereas inhibition of deciliation enhances cystic growth, indicating that cilia house pro-cystic signaling pathways, which in ADPKD remain unchecked. However, how mutations in *Pkd1* or *Pkd2* contribute to cyst formation/progression and especially, whether their inactivation impacts cilia structure and/or function remains unknown. Here, we examined whether the Polycystin complex has a role in cilia dynamics. Different cell types lacking *Pkd1* or *Pkd2* showed severely delayed deciliation, whereas ciliary assembly was unaffected. Consistently, the number of ciliated cells in the S phase, when cilia normally start resorbing, was increased in mutant cells *in vitro* and in the cystic epithelium of mice lacking *Pkd1*. Deletion of *Polycystins* led to upregulation of the p53 tumor suppressor as a result of the activation of the centrosomal integrity/mitotic surveillance (CI/MS) pathway, which is activated upon centrosomal loss. p53 inhibited deciliation via upregulation of the FBW7 E3 ubiquitin ligase, which promoted proteasomal degradation of NDE1, a negative regulator of cilia formation. Delayed deciliation in *Polycystin*-null cells caused persistent activation of cilia-based signaling pathways such as TGF $\beta$ /Smad, which contributes to cyst progression. When comparing mice lacking *Pkd1* or *Pkd1/Fbxw7*, both mouse strains had similar cystogenesis, however renal function was restored in double mutant mice, suggesting that renal function in ADPKD is not deteriorating due to physical expansion of cysts, but instead cystogenesis and renal function can be uncoupled. According to our model, deletion of *Polycystins* causes activation of the CI/MS pathway resulting in p53-mediated upregulation of FBW7 and downregulation of NDE1 and possibly other positive regulators of deciliation. Because of delayed deciliation, cilia-based signaling pathway(s) are abnormally overactivated leading to deterioration of kidney function that appears to be independent of cystogenesis.