EBioMedicine 61 (2020) 103043

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.elsevier.com/locate/ebiom

Commentary

Is autophagy the culprit of cystogenesis in polycystic kidney disease?

Shixuan Wang[a], Zheng Dong*,[a]

[a] Department of Cellular Biology and Anatomy, Medical College of Georgia, Augusta University and Charlie Norwood VA Medical Center, Augusta, GA 30912, USA

ARTICLE INFO

Article History:
Received 17 September 2020
Accepted 17 September 2020

Autosomal dominant polycystic kidney disease (ADPKD), the most common inherited human renal disease, results from mutations in either *PKD1* or *PKD2* gene. It is a progressive disease characterized by gradual cystogenesis and cyst enlargement in multiple organs, such as the kidney and liver. Despite intensive studies in the past several decades, especially after the identification of the responsible genes, the cellular and molecular mechanisms of ADPKD are still not well understood. A consensus is that increased cell proliferation is responsible for cyst formation and development. However, clinical trials with anti-proliferation drugs such as mTOR inhibitors failed to generate encouraging results in PKD patients [1,2]. Although these drugs are shown to be effective in reducing cyst number and size and improving renal function in animal models. Recently, autophagy has emerged as an important mechanism in PKD, in consideration of several observations: 1) mTOR is the negative regulator of autophagy and autophagy suppression has been reported in human PKD kidneys and animal models [3,4], 2) activation of autophagy alleviates cystogenesis, 3) polycystin-1 or -2 has crosstalk with autophagy system directly or indirectly by interacting with ATG (autophagy-related gene) proteins and 4) PKD is one of the ciliopathies, while primary cilia and autophagy regulate reciprocally [5–7].

In a study reported in *EBioMedicine*, Lee et al [8] made another attempt to elucidate the relationship between autophagy and PKD by taking advantage of different techniques and models. They first examined the expression profile of ATG genes using previously published microarray datasets derived from human ADPKD samples. In contrast to the previous report [3], they found a high expression of almost two-thirds of *ATG* genes in PKD human samples. This finding encouraged them to further explore autophagy in PKD using different animal models. Ablation of *ift46* specifically in collecting ducts led to PKD phenotype and activation of MAPK and mTOR signaling pathways, accompanied by a loss of cilia and increased cell proliferation and apoptosis. They also found the reduction of ATG proteins and dysfunctional autophagy in *ift46*$^{-}/^{-}$ models. To further study the role of autophagy in cystogenesis, they crossed *ift46*$^{-}/^{+}$ mouse with *Lc3b* transgenic mouse. It was found that *Lc3b* expression accelerated cyst formation in *ift46*$^{-}/^{+}$ mice. This was true also for the zebrafish model. In support, autophagy activation by starvation worsened the PKD phenotype while suppression of autophagy by 3-MA alleviated cyst development. To confirm the findings of the *ift46* mouse model, they also examined autophagy in *Pkd1* mice.

This study confirms the previous observation of abnormal autophagy in PKD. However, in contrast to the previous report [3], this study suggests that some PKD patients may have increased autophagy that contributes to cyst development. The finding raises concerns about the therapeutic potential of autophagy activators. If autophagy is suppressed in some PKD patients whereas increased in others, it is difficult to determine that autophagy activators or inhibitors are beneficial unless the drug is used in a personalised manner. This finding reminds us of the complexity of autophagy in PKD. Indeed, their finding is not alone. It was reported that autophagy was enhanced in polycystic kidneys with *Aqp11* mutation in mice [9]. Several aspects may be considered to explain the discrepancy between this study and other reports. First, these studies tested different experimental models. Especially, the *ift46*$^{-}/^{-}$ model used in this study is not a bona fide model of PKD, rather its direct effect is defective cilia or ciliopathy. Another important question is how to assess autophagy status in PKD. Generally, LC3B is a standard marker for autophagy by quantification and flux assay. However, given the discrepancy between this study and previous reports, it seems that more ATG genes at the protein level should be analyzed to have an overall view of autophagy status in PKD patients. Furthermore, signaling pathways, including those regulating autophagy, may differ at different stages or time of PKD, making it difficult to compare the results obtained from various experimental settings. Finally, when considering experimental drug administration, many factors have to be taken into account. For instance, the time, duration, and dosage may affect results. Although this study provides interesting information about autophagy in PKD patients, it is necessary to significantly expand the cohort and distinguish the underlying genotypes that may have an impact on autophagy. Such investigations would significantly advance the understanding of autophagy regulation, its pathogenic role, and therapeutic potential in PKD.

Contributors

Dr. Shixuan Wang and Dr. Dong wrote the manuscript.

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2020.102986.
* Corresponding author.
E-mail address: zdong@augusta.edu (Z. Dong).

https://doi.org/10.1016/j.ebiom.2020.103043

Declaration of Interests

Authors have nothing to disclose.

Acknowledgements

The authors were supported in part by grants from Department of Veterans Affairs (Merit Review Award I01 BX000319) and NIH (DK058831, DK087843) of USA. ZD is a recipient of Senior Research Career Scientist award from the Department of Veterans Affairs.

References

[1] Serra AL, Poster D, Kistler AD, et al. Sirolimus and kidney growth in autosomal dominant polycystic kidney disease. N Engl J Med 2010;363(9):820–9.

[2] Walz G, Budde K, Mannaa M, et al. Everolimus in patients with autosomal dominant polycystic kidney disease. N Engl J Med 2010;363(9):830–40.

[3] Belibi F, Zafar I, Ravichandran K, et al. Hypoxia-inducible factor-1alpha (HIF-1alpha) and autophagy in polycystic kidney disease (PKD). Am J Physiol Renal Physiol 2011;300(5):F1235–43.

[4] Shillingford JM, Murcia NS, Larson CH, et al. The mTOR pathway is regulated by polycystin-1, and its inhibition reverses renal cystogenesis in polycystic kidney disease. Proc Natl Acad Sci U S A 2006;103(14):5466–71.

[5] Wang S, Livingston MJ, Su Y, Dong Z. Reciprocal regulation of cilia and autophagy via the MTOR and proteasome pathways. Autophagy 2015;11(4):607–16.

[6] Tang Z, Lin MG, Stowe TR, et al. Autophagy promotes primary ciliogenesis by removing OFD1 from centriolar satellites. Nature 2013;502(7470):254–7.

[7] Pampliega O, Orhon I, Patel B, et al. Functional interaction between autophagy and ciliogenesis. Nature 2013;502(7470):194–200.

[8] Lee EJ, Ko JY, Oh S, et al. Autophagy induction promotes renal cyst growth in polycystic kidney disease. E Bio Med 2020 In PressAccess available https://10.1016/j.ebiom.2020.102986.

[9] Tanaka Y, Watari M, Saito T, Morishita Y, Ishibashi K. Enhanced autophagy in polycystic kidneys of AQP11 null mice. Int J Mol Sci 2016;17(12).