Cell Cycle 13:6, 869–870; March 15, 2014; © 2014 Landes Bioscience

Tuberin in renal cell hypertrophy

Samy L Habib

Department of Geriatrics; Geriatric Research, Education, and Clinical Center; South Texas Veterans Healthcare System; San Antonio, TX USA;
Department of Cellular and Structural Biology; University of Texas Health Science Center at San Antonio; San Antonio, TX USA

Renal hypertrophy is an important prognostic indicator of progression of renal disease. Tubular cells, in particular those of the proximal tubule, are primary targets of hyperglycemia. Chronic exposure of renal cells to high glucose resulted in elevation of blood glucose and contributed to the tubulointerstitial.[1] In diabetes, the renal tubule is subject to both direct and indirect insults. Renal enlargement is one of the first structural changes in diabetic nephropathy (DN) due to the hypertrophy of existing glomerular and tubular cells, rather than to cellular proliferation.[2] Increase in renal size is predominantly due to proximal tubular epithelial cell hypertrophy after a decrease in nephron number that may due to disease or surgical resection. The initial tubular epithelial cell hypertrophy is considered "compensatory" and "adaptive" hypertrophy.[3] In general, cell size determined by a balance between new protein accumulation and degradation of existing proteins. The rate of deterioration of kidney function shows a strong correlation with the degree of tubulointerstitial fibrosis.[4]

Tubular cells undergo hyperplasia or hypertrophy through 2 totally different growth responses. Several growth factors acting in concert are involved in this proliferative response of tubular cells. Each renal cell type has a different constitutive expression pattern of cell cycle proteins. The role of each cell cycle protein is probably cell type–specific and also depends on the form of injury, and, hence, its role in renal disease is not always predictable. In contrast to the mitogenic growth response of regenerating tubular cells, cellular hypertrophy is not well understood. Hypertrophic cells are arrested in the G_1–phase of the cell cycle and increase protein and RNA content, but do normally not replicate their DNA.[5] Such an enlargement of tubular cells often occurs in more chronic situations of renal damage, in which remnant nephrons adapt their function to the increasing need. However, evidence exists that hypertrophic tubules are finally joined into the process of maladaptation of renal function, leading to tubular atrophy, interstitial scarring, and progression of renal disease.[6]

Tuberin (encodes by *TSC2*) triggers mammalian cell size reduction, and a dominant–negative *TSC2* mutant induces increased cell size. In *Drosophila*, tuberin deficiency causes an increase in eye cell size.[7] Our recent study showed that tuberin is a key molecule that plays a major role in regulation of cell matrix protein in diabetes.[8] In addition, tuberin deficiency increases kidney size (27%) in $TSC2^{+/-}$ rats[8] and (20%) in $TSC^{+/-}$ mice (unpublished data) compared with wild–type rats and mice.[8] Tuberin is a direct substrate of Akt that involved in the regulation of insulin signaling pathway, which is a very important regulator of cell cycle and cell size control. This pathway includes also the FKBP12–rapamycin–associated protein mTOR and affects cell proliferation and cell size regulation. In addition, protein synthesis and protein degradation are coordinately regulated by mTOR pathway that are influenced by availability of nutrients and growth factors. Tubein blocks mTOR activity and decreased cell size due to inhibition of translation and decreased cell proliferation in mammals. On the other hand, deficiency in tuberin leads to activate of mTOR through upregulate its 2 downstream effectors: S6K (p70S6K) and 4EBP1 (eukaryotic initiation factor 4E–binding protein 1), which are required for biosynthesis of the cellular translational apparatus, a critical component for cell growth. Inhibition of mTOR by rapamycin resulted in decrease kidney size and cell matrix protein accumulation in kidney of tuberin–deficient mouse (unpublished data). Although these alterations in renal structure and size may occur and are not specific only to the kidney, it may reflect a consequence of long–standing diabetes/hyperglycemia. The pathological changes in glomerular and tubular cells are strongly correlated with glycemic control and occur independently of progressive DN. In addition, renal failure occurs in association with increase renal hypertrophy that may reverse following strict glycemic control for a few months.

In conclusion, the progressive decline in renal function in diabetes is ultimately due to the accumulation of extracellular matrix proteins and increased in cell hypertrophy, which may result from decreased tuberin expression. Therefore, understanding the mechanisms by which tuberin/mTOR pathway regulates of cell hypertrophy is the key to finding the therapeutic target to prevent the progression of renal damage and speeding up renal recovery after acute renal failure in diabetic patients.

Correspondence to: Samy L Habib; Email: habib@uthscsa.edu
Submitted: 01/16/2014; Revised: 01/17/2014; Accepted: 01/21/2014; Published Online: 02/02/2014
http://dx.doi.org/10.4161/cc.27942
Comment on: Habib SL, et al. J Am Soc Nephrol 2012; 23:1652-62; PMID:22904348; http://dx.doi.org/10.1681/ASN.2012030285

References

1. Brownlee M. Diabetes 2005; 54:1615-25; PMID:15919781; http://dx.doi.org/10.2337/diabetes.54.6.1615
2. Phillips AO, et al. Histol Histopathol 2002; 17:247-52; PMID:11813875
3. Zhang XL, et al. Am J Pathol 2004; 165:763-73; PMID:15331401; http://dx.doi.org/10.1016/S0002-9440(10)63339-1
4. Berthier CC, et al. Diabetes 2009; 58:469-77; PMID:19017763; http://dx.doi.org/10.2337/db08-1328
5. Wolf G. Kidney Int Suppl 2000; 77:S59-66; PMID:10997692; http://dx.doi.org/10.1046/j.1523-1755.2000.07710.x
6. Hodgkins KS, et al. Pediatr Nephrol 2012; 27:901-9; PMID:21947270; http://dx.doi.org/10.1007/s00467-011-1992-9
7. Potter CJ, et al. Cell 2001; 105:357-68; PMID:11348592; http://dx.doi.org/10.1016/S0092-8674(01)00333-6
8. Habib SL, et al. J Am Soc Nephrol 2012; 23:1652-62; PMID:22904348; http://dx.doi.org/10.1681/ASN.2012030285