Nature Reviews Nephrology **9**, 624 (2013); published online 1 October 2013; doi:10.1038/nrneph.2013.185

CHRONIC KIDNEY DISEASE

After nephron reduction, podoctyes get in on the AKT

Chronic kidney disease is characterized by the progressive loss of functional nephrons. The resulting increase in stress on the remaining nephrons leads to functional alterations, but these adaptations ultimately lead to further nephron loss in a vicious cycle. Although this situation has long been established, the mechanisms behind the progression of chronic kidney disease are not clear. In their preclinical study, Fabiola Terzi and coauthors now show that this process is intrinsically linked to podocyte viability, which requires expression of AKT2.

The three RAC serine/threonine-protein kinases (AKT1, AKT2 and AKT3) regulate a number of cellular functions, including apoptosis and cytoskeleton rearrangement, and seem to be positively regulated by the core proteins of the slit diaphragm. "We, therefore, speculated that AKT activation could allow podocytes to cope with the stress associated with nephron reduction," says Terzi.

Terzi explains their strategy: "we approached this question by applying different experimental models of nephron reduction to genetically modified mice carrying ... a germinal and/or a podocyte-specific inactivation of *Akt1*, *Akt2* or *Rictor* genes." In the glomeruli of partially nephrectomized wild-type mice (resulting in a 75% nephron reduction), phosphorylation of AKT was threefold higher than in controls. Furthermore, AKT2 was localized to the podocytes.

Building on these indications that AKT2 has a key role in podocytes, the researchers created *Akt2*-knockout mice. In these mice, nephron reduction induced more severe glomerular lesions and albuminuria than in wild-type mice. Further, in the $Akt2^{-/-}$ mice, levels of phosphorylated AKTs did not increase in the glomeruli, despite increased AKT1 expression.

These observations were of interest, but did not reveal the mechanism of action behind the apparent protective effect of AKT2 in stressed glomeruli. After ruling out hypertension and diabetes as causes, the possibility that AKT2 might have an intrinsic function in podocytes was investigated using $Akt1^{-/-}$ and $Akt2^{-/-}$ mice, as well as podocyte-specific *Akt2*-mutant mice. "We could show that nephron reduction led to the specific activation of AKT2 in podocytes in order to prevent cytoskeleton rearrangement, podocyte rarefaction, albuminuria and glomerular scarring. We also used *in-vitro Akt1* and *Akt2* short-hairpin RNA silencing, to complement our *in vivo* models, confirming the specific function of AKT2 in maintenance of the podocyte cytoskeleton," explains Terzi.

Having identified this crucial role of AKT2, the mechanism of activation of this protein was explored. In mice with podocyte-specific disruption of the mTorc2 protein complex (a well-known activator of AKTs), achieved by knocking out *Rictor*, AKT phosphoylation was significantly lower than in wild-type mice. This observation indicated that mTorc2 had a role in the activation of AKT2 in podocytes.

The translation of basic cell biology findings such as these to the clinic can often take considerable time; however, in this case the researchers were in luck. Patients receiving a kidney transplant are frequently treated with the immunosuppressive agent sirolimus, which is now known to inhibit mTORC2, as well as mTORC1. Thus, the impact of these findings could be assessed directly in such patients. Terzi elaborates: "Ascertaining the pathophysiological relevance of our findings to human chronic kidney disease was an important concern during this work. In this aim, we studied a cohort of kidney transplant recipients treated or not treated with sirolimus, displaying different stages of renal failure. A number of studies have reported that kidney transplant recipients might develop proteinuria upon sirolimus treatment, particularly those with reduced glomerumar filtration rate (that is, more severe nephron reduction), suggesting that, as in mice, AKT activation might be required for glomerular adaptation to nephron reduction."

Analysis of patient biopsy samples showed that AKT inhibition was closely correlated with albuminuria in the patients treated with sirolimus. Furthermore, mTORC2—and not the previously supposed culprit, mTORC1—was involved in this proteinuric effect.

Terzi summarizes the consequences of their findings in terms of human health as follows: "we have found an extremely sensitive biomarker—mTORC2/AKT2 activation in podocytes—to identify patients with the highest risk of developing proteinuria upon treatment with mTOR inhibitors; we provide a rationale for the development of a novel therapeutic strategy (specific mTORC1 or AKT1 inhibitors) to overcome the adverse effect of these compounds in patients with reduced renal function; and we have identified in AKT2 a novel therapeutic target to preserve glomerular function during chronic kidney disease."

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Original article Canaud, G. *et al.* AKT2 is essential to maintain podocyte viability and function during chronic kidney disease. *Nat. Med.* doi:10.1038/nm.3313