EBioMedicine 32 (2018) 5

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Commentary

Epithelial Signaling through the RUNX1/AKT Pathway: A New Therapeutic Target in Kidney Fibrosis

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Treatment of chronic kidney disease is a major health challenge worldwide. Current treatments aim to control blood pressure and proteinuria, especially through renin angiotensin aldosterone system inhibition [1]. Unfortunately, these treatments targeting the vascular and glomerular compartments of the kidney often fail to stop the progression of the disease. Another major contributor to chronic kidney disease is tubular cells. Specific activation of the renal tubular cells is sufficient to cause kidney fibrosis [2]. Changes in the pattern of gene expression in the renal epithelium is a hallmark of renal fibrosis in animal models and in human pathology. This process is named partial epithelial to mesenchymal transition (pEMT), as opposed to full EMT observed in carcinoma, where cells also acquire the ability to migrate out of their initial environment, thus facilitating metastatic dissemination of the disease [3]. Induction in the renal tubule of one master EMT regulator, *SNAI1*, is sufficient to cause kidney fibrosis, and reversal of pEMT by SNAIL1 inhibition is protective [4].

In this issue of *EBioMedicine*, Zhou and coworkers show that RUNX1 is induced in the renal tubule in 2 different models of chronic kidney disease, and causes kidney fibrosis through P110∂/AKT activation [5]. They show that the tubular-specific inhibition of this pathway is sufficient to control chronic structural damage, and in one model, to improve kidney function. They also use pharmaceutical compounds to target this pathway and block EMT in renal tubular cells *in vitro*. Interestingly, although the mRNA expression of the master EMT gene *SNAI1* preceded the induction of *RUNX1*, it needed RUNX1 expression for signal transduction, highlighting RUNX1 as a switch controlling the downstream fibrotic process. The fact that there is no significant basal expression of RUNX1 or P110∂ in the kidney, and that inhibitors of both P110∂ and PI3K are clinically tested for treatment of cancer is very encouraging in terms of potential therapeutic applications.

P110∂ inhibition is being evaluated in hematological malignancies (*e.g.*, NCT02457598). These ongoing studies will provide important safety data for this drug, and inform its potential chronic use for non-malignant diseases. Also, RUNX1 expression was found to be associated to tumors derived from renal proximal tubular cells, clear renal cell carcinoma [6], and targeting the PI3K/AKT pathway with inhibitors of the rapalog family has shown some (although limited) efficiency in these tumors. Considering the lack of efficient treatments for these tumors when complete surgical removal is not possible, upstream targeting of the RUNX1/P110∂/AKT pathway is a promising strategy.

Important developments are needed before these findings can be implemented to the clinical setting: is this RUNX1/AKT instrumental in other models of chronic kidney disease and in humans? In particular, Akt is induced in models of diabetic nephropathy, a major contributor to chronic kidney disease [7]. It will be important to assess the efficiency and the safety of inhibiting the p110∂/AKT pathway in these situations on the long term. Chronic kidney disease is often multifactorial, and superimposed episodes of acute kidney injury are frequent. Because chronic diseases require long-term treatment, it is needed to evaluate the time-dependent cumulative toxicity of such therapies, and to assess potential interactions with other medical conditions occurring in the population of patients with chronic kidney disease.

Disclosure

The author declares no conflicts of interest.

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DOI of original article: https://doi.org/10.1016/j.ebiom.2018.04.023.
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https://doi.org/10.1016/j.ebiom.2018.05.020