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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 inhi-

bition [1]. Unfortunately, these treatments targeting the vascular and

glomerular compartments of the kidney often fail to stop the progres-

sion 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 ini-

tial environment, thus facilitating metastatic dissemination of the dis-

ease [3]. Induction in the renal tubule of one master EMT regulator.

SNAI1, is sufficient to cause kidney fibrosis, and reversal of pEMT by

disease, and causes kidney fibrosis through $P110\partial$ /AKT activation [5]. They show that the tubular-specific inhibition of this pathway is suffi-

cient 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. Inter-

estingly, 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

(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

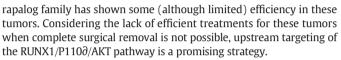
to tumors derived from renal proximal tubular cells, clear renal cell car-

cinoma [6], and targeting the PI3K/AKT pathway with inhibitors of the

P110∂ inhibition is being evaluated in hematological malignancies

very encouraging in terms of potential therapeutic applications.

In this issue of *EBioMedicine*, Zhou and coworkers show that RUNX1 is induced in the renal tubule in 2 different models of chronic kidney



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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SNAIL1 inhibition is protective [4].



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