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AMPK activity is a therapeutic target for treatment of non-diabetic CKD

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Objectives: This study investigates the impact of AMPK activity in a rat kidney ablation and infarction (A/I) model (also called STN, subtotal nephrectomy), the most commonly studied model of non-diabetic chronic kidney disease (CKD). The study tests the changes of renal AMPK activity in un-treated A/I rats and finds out the correlation of AMPK activity with such renal parameters as renal metabolic efficiency, kidney function and renal morphology; it then treats the A/I rats in three different ways -- ANG II blockade, HIF induction and direct AMPK activation by Metformin, to examine their effects on renal AMPK activity in relation to the renal parameters.

Methods: The A/I model is created by removing the right kidney and ligating two branches of the left renal artery. AMPK activity (p-AMPK-α) is tested by Western blot. GFR, RBF, renal oxygen consumption (QO2) and sodium transport (TNa) are measured using common techniques. ANG II blockade is created with captopril and losartan. HIF induction is achieved with DMOG. Kidney fibrosis is observed via histology.

Results: AMPK activity in A/I rats is decreased. The A/I kidney at one week exhibits reductions in renal metabolic efficiency and kidney function, accompanied by a significant decrease in AMPK activity. These parameters progressively worsen with time, and extensive kidney fibrosis occurs at four weeks.

Angiotensin II blockade and HIF-1 induction not only restore the AMPK activity but also correct kidney metabolic inefficiency, improved kidney function and ameliorate kidney fibrosis.

Induction of AMPK activity with metformin produces the same renal protective effects as the above two treatments, with no negative impact on blood pH, blood lactate or glucose levels.

Conclusion: Our results show that early decline of renal AMPK activity associates with declines of metabolic efficiency and kidney function and later progression of renal fibrosis. Three different treatments that restore renal AMPK activity all correct the abnormalities, regardless of their initial molecular pathways. We therefore propose that (1) AMPK activity is a valid indicator of the status of non-diabetic CKD; (2) deregulation of AMPK is a common pathway for the progression of non-diabetic CKD; and (3) induction of AMPK activity may thus prove an effective therapeutic target for the treatment of non-diabetic CKD.

Biography

Aihua Deng, M.D., Ph.D., combining three training backgrounds – internal medicine (medical school), physiology (Ph.D) and molecular biology (postdoc), has been devoted to nephrology research for over 20 years. In the past 16 years, she has been working in Dr. Roland Blantz's nephrology lab at UCSD (University of California San Diego). She is the first author of a number of publications on major nephrology-related journals, such as KI (Kidney International), JASN (Journal of American Society of Nephrology) and AJP (American Journal of Physiology).

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