Researchers link immune system to salt-sensitive hypertension in CKD

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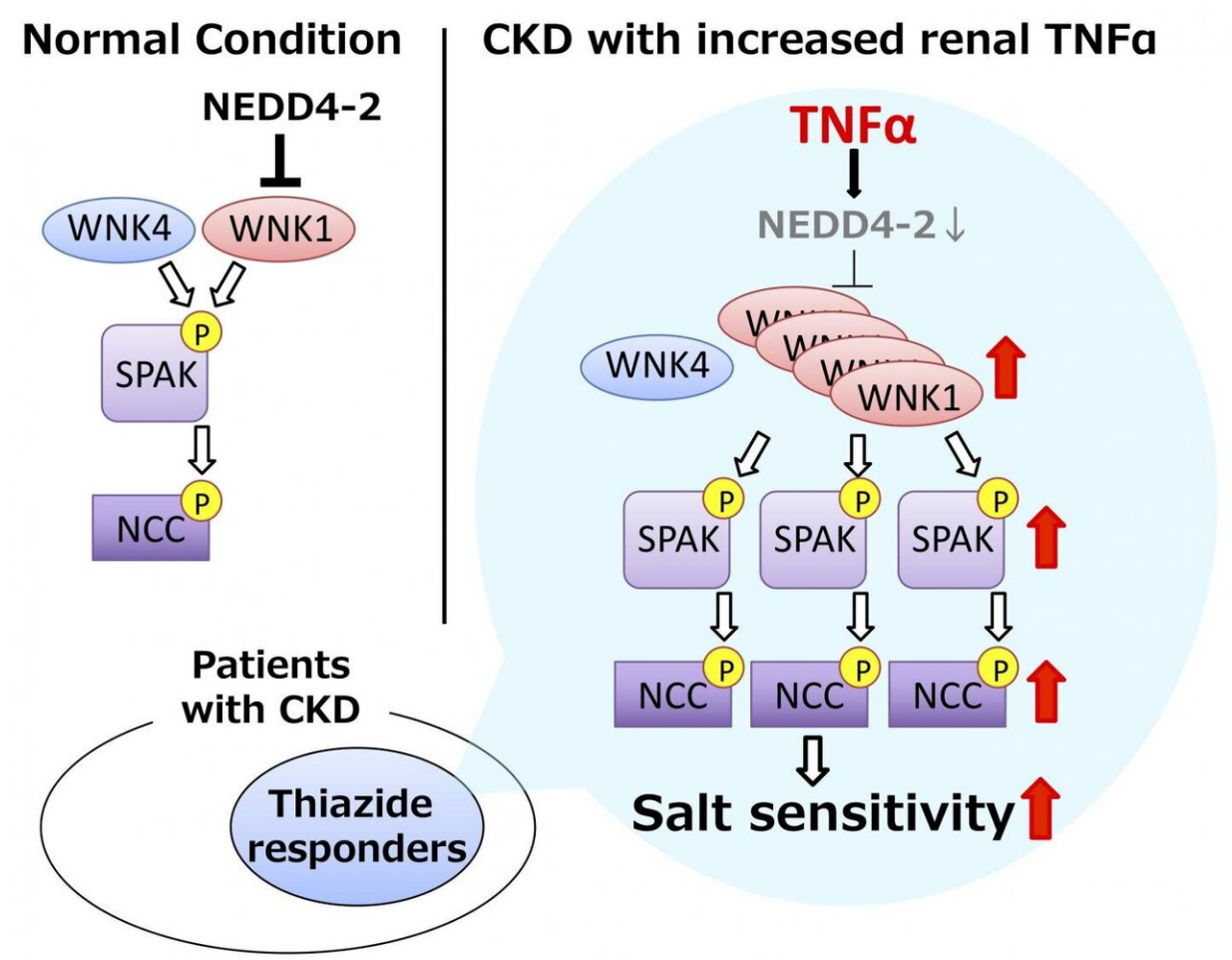

WNK phosphorylation cascade plays an important role in sodium handling in the distal nephron of the kidney. Over-activation of this pathway increases sodium reabsorption through NaCl cotransporter (NCC) and causes salt-sensitive hypertension. This study demonstrated that TNFα activates WNK1-SPAK-NCC phosphorylation cascade by suppressing NEDD4-2 which degrades WNK1,

contributing to salt-sensitive hypertension in CKD with increased renal TNFα. Therefore, WNK phosphorylation cascade may be a link between immune systems and hypertension. In addition, TNFα-WNK1-SPAK-NCC axis may be activated in patients with CKD for whom thiazide diuretics, NCC inhibitors, are effective. Credit: Department of Nephrology,TMDU

Researchers from Tokyo Medical and Dental University (TMDU) find that immune system signaling molecule TNF-α may trigger high blood pressure in patients with chronic kidney disease.

Detecting threats, sending out response molecules, and altering gene expression—our immune system works tirelessly day and night to protect us from invading pathogens and maintain general health and wellbeing. But in a study published this month in peer-reviewed journal *Kidney International*, a group of researchers from Tokyo Medical and Dental University (TMDU) in Japan have found a link between the immune system and high blood pressure in patients with chronic kidney disease (CKD).

CKD affects almost 800 million people worldwide and is the underlying cause of over a million deaths each year. One of the major complications of CKD is high blood pressure, or hypertension, and studies have shown that controlling blood pressure is an important factor in preventing CKD progression. However, many CKD patients display increased salt-sensitivity, a condition where blood pressure is unduly influenced by dietary salt intake, making it much harder to control.

Inappropriate over-activation of a pathway called the WNK-SPAK-NCC phosphorylation cascade increases salt reabsorption in the kidney, leading to salt-sensitive hypertension. However, whether this pathway causes hypertension in CKD patients and what regulates the

phosphorylation cascade had not been investigated.

Using a mouse model of disease, the researchers confirmed that mice with CKD had increased levels of the WNK1 protein in their kidneys, causing increased activation of the downstream proteins SPAK and NCC. When fed a high salt diet, the WNK-SPAK-NCC pathway remained activated in CKD mice, leading to salt-sensitive hypertension.

The researchers then looked to several recent studies suggesting that the immune system may play a role in salt sensitivity. Sure enough, levels of pro-inflammatory cytokine TNF-α were elevated in the kidneys of CKD mice, and provision of TNF-α resulted in increased levels of WNK1.

"Interestingly, TNF-α did not increase the transcription of WNK1, suggesting that it somehow prevented the degradation of mature WNK1 protein instead," says corresponding author of the study Dr. Eisei Sohara. "Based on this hypothesis, we confirmed that TNF-α enhances WNK1 protein levels by preventing the transcription of NEDD4-2 E3-ligase, a protein that normally degrades mature WNK1." By inhibiting TNF-α, the researchers were able to reverse the salt sensitivity of CKD mice fed a high salt diet, confirming the link between the immune system and salt sensitivity.

Thiazide diuretics, NCC inhibitors, are widely used antihypertensive drugs, but their efficacy varies among patients with CKD. To achieve precision medicine, it is important to predict the efficacy of medication beforehand. Patients with enhanced activity of NCC are considered to respond well to thiazide diuretics. Therefore, findings of this study may contribute to better choices of antihypertensives in the future.

More information: Taisuke Furusho et al, Renal TNFα activates the WNK phosphorylation cascade and contributes to salt-sensitive hypertension in chronic kidney disease, *Kidney International* (2020).

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