THE KOREAN SOCIETY OF NEPHROLOGY
APCN & KSN 2024
June 13(Thu) - 16(Sun), 2024 Coex, Seoul, Korea
APSN
Promoting Sustainable Kidney Health: The Asia-Pacific and Beyond

Abstract Submission No.: A-0654

Lipocalin-2 promotes cardiovascular calcification in chronic kidney disease by upregulating NCOA4-mediated ferritinophagy and ferroptosis through STAT3 signaling activation

Yujia Wang[1], Rining Tang[2]
[1]Department of Internal Medicine-Nephrology, Institute of Nephrology, Zhong Da Hospital, Southeast University, School of Medicine, Nanjing, China, China
[2]Department of Institute of Nephrology, Institute of Nephrology, Zhong Da Hospital, Southeast University, School of Medicine, Nanjing, China, Institute of Nephrology, NanJing LiShui Peoples Hospital, Zhongda Hospital Lishui Branch, Southeast University, School of Medicine, Nanjing, China, China

Objectives : Cardiovascular calcification (CVC) is an insidious complication of chronic kidney disease (CKD), contributing to the high cardiovascular morbidity and mortality seen in this population. Recent evidence implicates ferroptosis, a form of programmed cell death, and ferritinophagy, particularly involving nuclear receptor coactivator 4 (NCOA4), in the pathogenesis of CKD-CVC. Lipocalin-2 (LCN2), an iron-modulating protein linked to osteogenesis and ferroptosis, has emerged as a potential contributor to CKD-CVC, yet its role remains to be fully elucidated.
Methods : To assess the involvement of LCN2 in CKD-CVC, a cross-sectional clinical study evaluated its expression in patient serum and calcified arteries. Animal models, including LCN2 knockout mice and mice with VSMC-targeted LCN2 manipulation, were fed a high adenine and phosphate diet to induce CKD-CVC. In vitro, VSMCs underwent LCN2-related treatments to delineate its function. Calcification was assessed using von-Kossa and Alizarin Red staining, while molecular changes were analyzed through PCR, western blotting, and other biochemical assays.
Results : LCN2 expression was positively associated with the severity of CKD-CVC. Dietary induction of CKD-CVC in vivo led to significant renal and cardiovascular calcification. In vitro, exposure to a high phosphate medium resulted in VSMC calcification and osteogenic differentiation, alongside enhanced ferroptosis indicators, such as increased iron accumulation and oxidative stress. Inhibiting ferroptosis pharmacologically reversed these effects. LCN2 knockout mice exhibited less calcification, suggesting a causative role of LCN2 in CKD-CVC. Mechanistically, LCN2 influenced NCOA4 and FTH1 expression levels, implicating ferritinophagy in the calcification process, with NCOA4 knockdown ameliorating the effects.
Conclusions : LCN2 is involved in the pathophysiology of CKD-CVC via modulation of VSMC ferroptosis and osteogenic differentiation. Targeting the LCN2/STAT3/NCOA4/FTH1 axis could offer a promising therapeutic strategy for managing CKD-CVC.