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

Abstract Submission No.: A-0128

Deficiency of GADD45a Expression Mediated Tubulointerstitial Injury in Diabetic Nephropathy

Xueqi Li[1], Jia Xiu Zhang[1], Liang Li[1], Qin Yi Wu[1], Kun Ling Ma[2]
[1]Department of Internal Medicine-Nephrology, Southeast University, China
[2]Department of Department of Nephrology, the Second Affiliated Hospital, School of Medicine, Zhejiang University,, China

Objectives : Recently, the disorder of mitochondrial fatty acid β-oxidation in proximal tubules has been reported to play crucial roles in tubulointerstitial injury of diabetic nephropathy (DN). The GADD45α plays a crucial role in various cellular processes, including mitochondrial biogenesis and lipid metabolism. Recent studies have demonstrated that GADD45α facilitates gene activation by inducing DNA demethylation. Therefore, this study aimed to investigate the role of GADD45α in tubulointerstitial injury of DN and its underlying mechanisms.
Methods : Bioinformatics and machine learning techniques were employed to identify differentially expressed genes between healthy individuals and DN patients. Experiments were conducted by using high glucose-treated HK-2 cells and streptozotocin (STZ)-induced mice. Lentivirus carrying the GADD45α gene was used to induce GADD45α overexpression in HK-2 cells. Adeno-Associated Virus vectors carrying LoxP-flanked GADD45α were intravenously injected into γGT-Cre transgenic mice to overexpress GADD45α in proximal tubules.
Results : Through bioinformatics and machine learning, GADD45α was identified to exhibit a strong association with tubulointerstitial injury in DN. Further analysis revealed that the expression of GADD45α was decreased in the kidneys of DN patients, diabetic mice, and high glucose-treated HK-2 cells. Notably, GADD45α overexpression ameliorated kidney damage and mitochondrial injury, leading to improved fatty acid β-oxidation, restored ATP production, and reduced ROS production. Transcriptomics analyses further demonstrated that GADD45α overexpression enhanced the expression of genes related to mitochondria with STEAP4 being a key protein in this process. Knocking down STEAP4 using siRNA in HK-2 cells exacerbated the damage induced by high glucose. In addition, our further results indicated that GADD45α overexpression decreased methylation of the STEAP4 promoter and increased STEAP4 expression.
Conclusions : GADD45α expression are reduced in DN, leading to tubulointerstitial injury. Overexpressing GADD45α can increase STEAP4 expression by demethylating. This enhances fatty acid oxidation, energy production, and reduces ROS production, thereby mitigating tubular injuries.Targeting the GADD45α-STEAP4 pathway holds potential as a therapeutic strategy.