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Inhibition of STAT3 mitigates fibrosis development in AKI-to-CKD by enhancing anti-oxidative responses

Ji Won Lee[1], Kyu Hong Kim[1], Hongbeom Park[1], Mi Yeon Yu[2], Sunhwa Lee[3], Yong Chul Kim[4], Dong Ki Kim[3], Yon Su Kim[4], Seung Hee Yang[5]
[1]Department of Biomedical sciences, Seoul National Unversity, Korea, Republic of
[2]Department of Internal Medicine-Nephrology, Hanyang University Guri Hospital, Korea, Republic of
[3]Department of Internal Medicine-Nephrology, Kangwon National University Hospital, Korea, Republic of
[4]Department of Internal Medicine-Nephrology, Seoul National University Hospital, Korea, Republic of
[5]Department of Kidney Reserach Institute, Seoul National University Medical Research Center, Korea, Republic of

Objectives : The Signal Transducer and Activator of Transcription 3 (STAT3) pathways are crucial in directing the transcriptional and physiological changes necessary for fibrosis development. The progression from AKI to CKD involves a complex network of multiple signaling pathways. Therefore, we evaluate the role of STAT3 using adenine-induced nephrotoxicity fibrogenesis.
Methods : C57BL/6 (8W, male) mice were injected orally with 2 mg of adenine daily for 14 days. To assess the anti-fibrotic properties of stat3 inhibition, stattic (10mg/kg, I.P, every other day) was administered one hour before the first adenine administration. In human proximal tubular cells, 1,2 and 4 mM adenine were treated with two different doses of stattic (0.5 and 1 μM) for 24 and 48 hours. Annexin-PI staining, western blot analysis, and immunohistochemistry were utilized to determine the involvement of STAT3 signaling in fibrogenesis.
Results : In mice treated with stattic, there was a significant reduction in serum creatinine and BUN levels compared to the group treated with adenine alone, indicating an improvement in renal function. The treatment also leads to decreased collagen deposition and lowered NGAL and F4/80 expressions in the tubulointerstitial areas. Furthermore, molecular analysis revealed an increase in Nrf2, an essential anti-oxidative transcription factor, while Cytc and Bax2 levels were decreased in stattic-treated mice. Sequentially, there was a reduction of phosphorylated p65, FN, and α-SMA expressions in mouse kidney and proximal tubular cells in a dose-dependent manner. Apoptotic cells were decreased in human proximal tubular cells being treated with stattic.
Conclusions : Targeting the STAT3 signaling pathway presents a viable anti-oxidative and anti-fibrotic approach, effectively delaying AKI-to-CKD progression.