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STAT3 Inhibition Restores Dysregulation of Kidney Capillaries by Modulating Angiogenesis

Kyuhyeon Kim[1], Jae Woo Park[2], Ji Won Lee[1], Sunhwa Lee[3], Eunjin Bae[4], Mi Yeon Yu[5], Dong Ki Kim[6], Kyu Ho Kang[2], Yon Su Kim[6], Seung Hee Yang[7]
[1]Department of Department of Biomedical Sciences, Seoul National University, Korea, Republic of
[2]Department of Department of Biological Sciences and Biotechnology, Chungbuk National University, Korea, Republic of
[3]Department of Internal Medicine-Nephrology, Kangwon National University Hospital, Korea, Republic of
[4]Department of Internal Medicine-Nephrology, Gyeongsang National University Changwon Hospital, Korea, Republic of
[5]Department of Internal Medicine-Nephrology, Hanyang University Guri Hospital, Korea, Republic of
[6]Department of Internal Medicine-Nephrology, Seoul National University Hospital, Korea, Republic of
[7]Department of Department of Kidney Research Institute, Seoul National University Medical Research Center, Korea, Republic of

Objectives : Signal Transducer and Activator of Transcription 3 (STAT3) is a multifunctional transcription factor that regulates key cellular processes involved in renal fibrosis. Our previous studies showed that inhibiting STAT3 alleviates fibrosis by reducing inflammation and apoptosis. However, its role in angiogenesis, which maintains crucial capillary networks, remains unclear. In this study, we harnessed single-cell RNA sequencing (scRNA-seq) to explore the impact of STAT3 on angiogenesis in adenine-induced renal fibrosis.
Methods : Adenine (2 mg/mouse, daily) and the STAT3 inhibitor Stattic (10 mg/kg, every other day) were administered to male C57BL/6 mice for 5 and 14 days to induce renal fibrosis. Kidneys and spleens were harvested for histological analysis and Western blotting. For scRNA-seq, RNA libraries were prepared with 14-day kidneys using the Illumina NovaSeq 6000 system. Differential gene expression analysis and downstream bioinformatics analysis were then conducted.
Results : STAT3 inhibition reduced serum creatinine levels elevated by adenine and restored kidney morphology. Histological analysis and Western blots confirmed that targeting STAT3 alleviated adenine-induced fibrosis, with decreased expression of pSTAT3 and pro-inflammatory markers. In the spleen, systemic inflammation markers were reduced. At the single-cell level, distinct kidney cell populations, including glomerular endothelial cells (GECs), were identified. STAT3 blockade restored kidney parenchymal cell populations while reducing fibroblasts and myeloid cells. Notably, the GEC population was significantly restored, exhibiting one of the strongest STAT3 pathway response and reestablished interactions with podocytes. Two GEC subpopulations, GEC0 and GEC1, were identified, with GEC1 showing enhanced angiogenesis-related gene expression and higher levels of gnaq and akap13, genes regulating endothelial function and proliferation, both reduced by inhibiting STAT3. CD31 staining revealed tubular atrophy and fragmentation in GECs from adenine-treated kidneys, while those under STAT3 inhibition appeared elongated and preserved integrity.

Conclusions : Targeting STAT3 activity emerges as a promising therapeutic strategy for chronic kidney disease by restoring GEC composition and regulating angiogenesis.