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STAT3 blockade ameliorates LPS-induced acute kidney injury through macrophage-driven inflammation

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Objectives : Signal transducer and activator of transcription 3 (STAT3) plays a pivotal role in regulating inflammation during the progression of acute kidney injury as a key transcription factor. Although several studies have elucidated the role of STAT3 in macrophage polarization, the exact mechanism and comparison between STAT3-related macrophage subtypes in kidney remain unclear. In this study, we investigated the role of macrophage-associated STAT3 controlling pro-inflammatory dynamics in acute kidney injury.
Methods : LPS-induced acute kidney injury (L-AKI) mice (C57BL/6) model was established by the intraperitoneal injection of LPS (10mg/kg) 6-24 hours before sacrificing. To examine the effect of STAT3 blockade, we administered Stattic (JAK2/STAT3 pathway inhibitor, 10mg/kg) 1 hour prior to LPS induction. Macrophage phenotypes were compared in each group by FACS analysis. In addition, mRNA sequencing was performed to study the transcriptome profiles of the L-AKI mice compared with Stattic-treated mice.
Results : Stattic treatment diminished the secretion of pro-inflammatory cytokines, reduced macrophage infiltration, and lowered the expression of markers associated with acute kidney injury in the L-AKI mouse model. FACS analysis revealed a significant shift within the intrarenal macrophage subpopulations: the predominance of CD11b ^{high} F4/80 ^{low} cells was decreased following Stattic treatment, while the CD11b ^{low} F4/80 ^{high} population restored to levels observed prior to LPS administration. To understand how Stattic modulates macrophage-driven inflammation in L-AKI kidney, we analyzed 1414 down-regulated genes using KEGG and GO enrichment analyses. Notably, three common genes (IL-6, Akt3, Pik3r1) were discovered in JAK-STAT, TLR, and TNF signaling pathway which downregulate macrophage mediated-inflammation. The expression of mRNA closely involved in macrophage phenotypes was increased by LPS stimulation and alleviated by Stattic treatment, along with the expression of STAT3-associated transcriptome.
Conclusions : Blockade of STAT3 effectively mitigated inflammation by retrieval of CD11b^{low} F4/80^{high} population, further emphasizing the role of STAT3-associated macrophage-driven inflammation in the progression of acute kidney injury.